PNEUMONIA IN THE NEWBORN

A Study of the Pathology and Bacteriology

of 177 Cases.

by

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PART I.

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INTRODUCTION.

It is only within comparatively recent years that the prevalence of pneumonia among newborn babies has begun to be recognised. Formerly it was regarded as a rarity, but the results of several investigations of large series of necropsy cases have proved that it is one of the principal causes of neonatal death. In spite of this it is probable that the great frequency of this disease has not yet been fully realised and that even now the problem of preventing it receives less attention than it deserves in view of its vital importance. This may be in part explained by a lack of clear knowledge of the causes and pathogenesis of neonatal pneumonia, for in spite of a considerable amount of pathological study there is still much doubt and disagreement as to the mode of infection, the relative importance of infection acquired before and after birth, the principal causative bacteria, and on other fundamental questions. It is probable that a fuller understanding of the pathological processes concerned and of the special circumstances of the neonatal period that influence the development and course of respiratory infection might lead to the more general adoption of preventive measures for the control of this common and dangerous disease.

The present investigation has been carried out

with these objects in view, in the hope that a study, more detailed than has hitherto been undertaken, of the pathological features and bacteriology of pneumonia and related pulmonary infections occurring before birth and during the first four weeks of postnatal life, might shed some fresh light on certain aspects of this subject and indicate some of the lines along which the problem of prevention might profitably be approached.

REVIEW OF THE LITERATURE.

Early references to neonatal pneumonia in the literature are mostly in the form of reports of isolated cases as interesting rarities. Gordon and Lederer (1928) state that Thorner (1884) was the first to describe a case of 'congenital pneumonia'. Netter (1889) reported the case of an infant whose mother was suffering from lobar pneumonia at the time of delivery, and who died at the age of five days with lobar pneumonia of the right upper lobe, pericarditis and meningitis. He ascribed the pneumonia in the infant to transplacental transmission of the pneumococcal infection from the mother, and quoted several similar cases previously reported by other observers. Most of the early publications refer to cases of this kind.

It was not until much later that the real frequency of pneumonia in the newborn began to be realised. Among the first to draw attention to the true facts was Hess-Thaysen (1914), whose paper still remains a valuable contribution to the subject and whose classification has been followed by a number of later workers. In a series of 111 necropsy cases of children under two months old at death he found 33 cases of pneumonia (29.7 per cent.). He emphasised the difficulty of diagnosing neonatal pneumonia by macroscopic examination only, expressing the opinion

that in many cases that are diagnosed as atelectasis pneumonia may be present although it is missed by the observer. In proof of his contention that many cases are missed unless special attention is given to its detection, he quoted the results in two series of his own cases. In the first series of 49 cases, when less care was taken, 4 cases of pneumonia were found (8 per cent.); whereas in a later series of 32 cases, when special attention was given, there were 14 cases of pneumonia (42 per cent.). This difficulty of detecting pneumonia in the lungs of the newborn and stillborn is the common experience of all workers in this field and is one of the principal reasons for the tardy recognition of the disease as one of the most important causes of neonatal death.

In several large series of cases investigated by later workers the percentage in which pneumonia was found has varied but has always reached a relatively high figure. The figures quoted by various workers are not strictly comparable, as some include only those born alive while others include stillbirths also, and there is some variation in the age period considered.

Browne (1921) found 21 cases (26 per cent.) among 80 cases of neonatal death and, as reported in a later publication (1922), 48 cases (31 per cent.) among 153 neonatal deaths. Johnson and Meyer (1925)

had 97 cases of pneumonia (19.4 per cent.) among 500 still-births and neonatal deaths up to the age of one month. Chase (1935) had 97 cases (21.8 per cent.) among 445, and Cruickshank (1930) 197 (24.5 per cent.) among 800 infants up to one month old. Helwig (1933) reported 66 cases of pneumonia (41.5 per cent.) in a series of 159 necropsies on stillborn and newborn infants, but he seems to have included cases in which there was evidence of aspiration of liquor amnii without any inflammatory cellular exudation. Kaldor (1933) had 12 cases of pneumonia (30.8 per cent.) among 39 still-births and neonatal deaths; Warwick (1934) had 43 (18 per cent.) in 240 necropsies on still-births and newborn infants up to two weeks old. Ylppö (1919) on the contrary, having studied 175 post-mortem cases, concluded that pneumonia is rare in the early days of life and becomes important only after two weeks. It is clear however that he relied too much on macroscopic observations.

Many workers have interested themselves in the mode of infection and their studies have led them to different conclusions regarding the relative importance of infection acquired before and after birth, and of the various ways in which prenatal or intranatal infection might occur. In the case of babies born alive the obvious difficulty arises of determining the time of infection - whether before, during or

after birth. Hess-Thaysen (1914) believed that babies already infected when born were unlikely to survive for more than three or four days. He therefore set the limit for what were to be regarded as birth infections at three days, it being impossible to exclude postnatal infection in those who survived longer. This limit has been accepted by a number of later workers, though some (e.g. Cruickshank, 1930) attached more importance to postnatal infection even in cases of very early death, and others believed that a child infected before birth might survive more than three days. Chase (1935) gave an average of six days for cases in his own series that he attributed to birth infection.

Most of the workers in this field have concentrated their attention particularly on pneumonia in the first few days of life and on the problem of determining what part is played by infection received during the process of birth. Hess-Thaysen (1914) was of opinion that undoubtedly the commonest cause was aspiration of infected material into the lungs before or during birth. He considered that infected liquor amnii was of less importance than bacteria-laden secretion in the birth passage which, he believed, might infect the infant not only when the vagina was diseased but also when it was normal. Browne (1921 and 1922) was impressed with the importance of long labour

and premature rupture of the membranes as a factor predisposing to infection of the foetus, by permitting bacteria from the vagina to invade the ruptured amniotic sac and to enter the nose and mouth of the foetus by aspiration or by direct surface growth. He was confirmed in this opinion by finding, in a small number of cases in which the bacterial cause was investigated, that Bact. coli was the commonest infecting organism.

Many have attached great importance to aspiration of amniotic fluid. Liquor amnii in the lungs can be recognised under the microscope by solid constituents present in it, such as cornified epithelial cells and lanugo hairs from the skin of the foetus, and sometimes masses of fat-laden vernix caseosa, or meconium. There is general agreement that in cases of pneumonia in the stillborn and newborn an excessive amount of amniotic debris is often found in the lungs. Hook and Katz (1928) found masses of aspirated amniotic sac contents in all cases (22) regarded by them as 'congenital pneumonia'. Kaldor (1933) also found amniotic debris in all his cases (12) of pneumonia in the stillborn and newborn. He was of opinion that every case of pneumonia associated with aspiration of liquor amnii should be regarded as congenital. Johnson and Meyer (1925) found evidence of aspiration in a large number of cases in which death occurred be-

fore, during, or within 3 days after birth. Warwick (1934) found it in 38 (88 per cent.) of 43 cases of pneumonia in stillborn foetuses and newborn infants up to two weeks old.

There has been considerable controversy as to what part is played by aspirated amniotic sac contents in the production of pneumonia. It is certain that large quantities may be present in the absence of any inflammatory reaction; it has been found in otherwise healthy lungs as long as two to three weeks after birth; its presence is therefore not of itself a sufficient cause of pneumonia associated with it. Yet it has been suggested that in certain circumstances uninfected amniotic fluid may act as an irritant and evoke and inflammatory reaction in the lungs. This is based upon the fact that some observers have failed to demonstrate bacteria in lungs that are the seat of pneumonia accompanying amniotic aspiration. Helwig (1933) for example found no bacteria in cases of stillbirth even when acute inflammation was present, but in the lungs of those who had lived twelve hours or more bacteria were found, which he inferred to be postnatal invaders of lungs predisposed to infection by the presence of amniotic fluid. He suggested that liquor amnii itself sometimes acts as an irritant, especially when it contains meconium. Kaldor (1933) believed that the irritant is chemical

rather than bacterial. Warwick (1934) found bacteria in Gram-stained sections of lung in only 11 of 43 cases and concluded from this that bacteria are probably not always the cause of the inflammatory reaction. He suggested that liquor amnii may vary in irritant effect, that alterations of its reaction or the presence of bile salts from meconium passed by an asphyxiated foetus might enhance its power to cause an inflammatory response, and that mechanical irritation might be produced by cornified cells in it. Snyder and Rosenfeld (1937) also believed that cells, sebaceous material and meconium may be injurious not only as foreign bodies but also as chemical irritants. Johnson and Meyer (1925), although inclined to the view that uninfected liquor amnii cannot cause inflammation, encountered the same problem. Using Gram-stained sections of lung they failed to find bacteria in many cases of the kind under consideration, and suggested that chemical antiseptics used for douches might sometimes be responsible for pneumonia in the child. On the other hand Hook and Katz (1928), though reaching no conclusion on this question, found that the aspirated masses usually contained bacteria and argued that failure to find them does not prove their absence. Johnson and Meyer (1925) found acute inflammation of the placenta and membranes in a high proportion of cases in which these were examined, and

held that this confirmed the importance of infection of the amniotic fluid. Farber and Sweet (1931), in a study devoted to amniotic sac contents in the lungs of infants, found that these evoked extraordinarily little reaction and that polymorphonuclear leucocytes appeared only when bacteria were present. Tow (1937) stated that aspiration of liquor amnii is the most frequent cause of pneumonia in the newborn, especially if it is infected. Hess-Thaysen (1914) on the contrary was of opinion that aspirated liquor amnii had no connection with pneumonia, while Cruickshank (1930) considered its presence important as a factor predisposing to postnatal infection.

Few later workers have given much credence to Hess-Thaysen's view of the importance of aspiration of infected vaginal secretion. Johnson and Meyer (1925) thought it unlikely. Most of the other workers quoted paid little attention to it, evidently being more impressed with the importance of aspirated liquor amnii. Chase (1935), however, considered that the large number of cases in his series that were free from obstetrical abnormalities and from evidence of infection of the liquor amnii suggested that the child became infected in the birth canal rather than in the uterus.

Most authors referred to the possibility of infection of the foetus by the transplacental route from the maternal to the foetal blood. This is known to oc-

cur in certain diseases, among which syphilis is the outstanding example. In a paper by Gordon and Lederer (1928) there are references to reported cases of intra-uterine infection with scarlet fever, smallpox and typhoid fever. Cases of pneumonia that have been ascribed to this mode of infection have been for the most part pneumococcal lobar pneumonia in infants born of mothers who were suffering from lobar pneumonia at the time of delivery (Netter (1889), Macdonald (1911), Gordon and Lederer (1928)). Lauche (1927) collected 9 authenticated cases from the world literature and 2 other probable cases, including one mentioned by Johnson and Meyer (1925). Lauche however inclined to the view that the child became infected, not through the blood, but through the bronchi by aspirating liquor infected with pneumococci. Johnson and Meyer (1925) believed transplacental infection to be rare. Tow (1937) thought that infection of the child after birth by contact with a mother suffering from pneumonia was more likely than haematogenous infection, but this does not explain the cases in which the pneumonia in the child was too far advanced to have begun after birth. Hook and Katz (1928) also had little belief in the transplacental route and considered that certain cases reported as due to transplacental haematogenous infection were not necessarily examples of postnatal infection, as the child had

lived several days and so might have been infected after birth.

A study of the literature on pneumonia in the first days of life thus reveals considerable difference of opinion, with a majority of workers favouring aspiration of infected liquor amnii as the commonest method of infection, some favouring other methods of prenatal infection, and a few, notably Cruickshank (1930), emphasising the greater importance of infection after birth.

The attention that has been given by research workers to pneumonia in slightly older infants in the neonatal period has been scanty compared with that given to cases in the first days of life, though several who studied large series included babies up to four weeks old or more. There is general agreement that the prevalent type is bronchopneumonia and the route of infection respiratory. Cruickshank (1930) found that the appearances in bronchopneumonia in the newborn were often modified by congestion, haemorrhage and atelectasis which might be present in the lungs before the onset of pneumonia, and that the gross appearance of patches often resembled lobar pneumonia. Holt and McIntosh (1933) described under the name of 'lobular pneumonia' a type occurring in young infants, though not confined to the neonatal period: the areas of consolidation, which are multi-

ple, 'encompass many lobules - - - but are not in immediate relation with bronchi and the walls of the latter and the interlobular septa are not thickened', the absence of interstitial inflammation being the distinguishing feature between this type and true bronchopneumonia. Most authors do not draw any distinction between lobular pneumonia and bronchopneumonia. True lobar pneumonia is recognised to be rare. Lauche (1927) asserted that, apart from the congenital cases already referred to, no case had been reported in a child under six months of age. He explained this on the ground that the characteristic reaction of lobar pneumonia occurs only in persons who have acquired a certain degree of sensitisation; therefore it cannot arise until a child has lived long enough to have become allergic from previous pneumococcal infection unless, in the case of newborn babies, the allergic state is transmitted from the mother. Hadfield and Garrod (1938) gave a summary of other observations supporting this idea and, while of opinion that the allergic hypothesis has not been fully proved, conceded 'the inevitable fact - - - that the development of lobar pneumonia seems to require a pre-existent humoral immunity', which necessarily implies either previous exposure to pneumococcal infection or passive immunisation.

Cruickshank (1930), while of opinion that most

cases are essentially of bronchopneumonic type, described two groups, atelectatic and septic. The first occurs in incompletely expanded lungs at any age in the neonatal period from the second day onward; the second usually in fully expanded lungs, resembling the bronchopneumonia of older infants and often accompanied by evidence of septicaemia in the form of multiple lesions in other parts of the body. Cruickshank's septic type is thus apparently not identical with the septic type of Hess-Thaysen (1914), which that author attributed to birth aspiration of septic material.

In addition to pneumonia due to respiratory tract infection, the classification of Hess-Thaysen (1914) and the modifications of it adopted by Chase (1935) and others include a group of extra-uterine metastatic infections in which the lungs are involved by way of the blood stream. According to Cruickshank (1930) the commonest sources of generalised blood infection are the skin and the respiratory tract; the umbilicus he found to be an uncommon source. In the modern literature only occasional cases of septicaemia are traced to infection of the umbilicus, but it was suggested by Friedländer (1927) that organisms may enter by the umbilicus without local signs of inflammation. Ylppö (1919) attached great importance to the gastro-intestinal tract as a source of general sepsis,

believing that bacteria enter the circulation at the site of haemorrhages in the gastro-intestinal mucosa. Lungs involved in a metastatic infection are described by Chase (1935) as uniformly solid or containing nodules which are not related to bronchi and at a later stage tend to form pyaemic abscesses.

With regard to the composition of the exudate in neonatal pneumonia, many observers are agreed that any large formation of fibrin is unusual though it may be present in small amount. There is some difference of opinion as to the cell content. Several authors note the absence or scarcity of polymorphonuclear leucocytes. Browne (1921 and 1922), describing 'catarrhal pneumonia', noted that there were usually very few polymorphs and concluded that this showed that in the young child there is little or no defence against infection. Ylppö (1919), who found that gross pneumonia was rare in the first days of life, considered that haemorrhage was more prominent than pure inflammatory processes in the lungs owing to the poor reaction of the newly born to infection; he attributed the haemorrhage to bacterial action. Müller and Bayer (1934) also referred to the poor ability of the newborn to produce an inflammatory reaction; and Gordon and Lederer (1928), in their report of a case of lobar pneumonia, described an absence of cells in the exudate in the consolidated lung. On the other

hand Cruickshank (1930), Hook and Katz (1928) and others found abundant polymorphonuclear leucocytes in the exudates.

Extensive haemorrhage in association with neonatal pneumonia has been noted by several workers (Johnson and Meyer (1925), Hintner (1927)). Browne (1921 and 1922) described 'acute haemorrhagic pneumonia' as a special type: death occurred suddenly and the lungs were found filled with blood recently poured out into the alveoli, without cellular exudation. Browne considered that this represented the early congestive stage of acute inflammation, the delicate blood vessels of the newborn infant giving way before the inrush of blood, and he believed that most cases had a bacterial cause but suggested that some might be anaphylactic. From the description it is not certain that the process was inflammatory. Thomson (1926) also referred to haemorrhagic pneumonia with very few polymorphonuclear leucocytes in the exudate. Cruickshank (1930) considered the haemorrhagic form to be a modification of ordinary pneumonia depending on severe asphyxia.

The occurrence of suppuration in the lungs as a result of neonatal pneumonia was said by Cruickshank (1930) to be more common than might be imagined. Chase (1935) mentioned abscess formation in cases of metastatic infection of the lungs. Johnson and Meyer

(1925) found abscesses in four cases of postnatal infection, two of which were metastatic. The majority of authors make little or no reference to asbcess formation.

Pleurisy, according to Cruickshank (1930), is often associated with neonatal pneumonia and may be serous, fibrinous or purulent; purulent pleurisy may occur in cases of septicaemia; large effusions and empyema are rare. Case reports of empyema are scarce in the literature. One such, in a child three days old, was published by Dodds (1928), who commented on the rarity of empyema in the newborn. Tow (1937), on the contrary, considered that empyema is not uncommon following pneumonia or rupture of a lung abscess.

Surprisingly little work has been done on the bacteriology of pneumonia in the newborn and dead-born. Complete bacteriological reports in the literature refer only to isolated cases. None of the workers who studied large series undertook a thorough bacteriological investigation, although Browne (1921 and 1922), Johnson and Meyer (1925), Hook and Katz (1928), Cruickshank (1930) and Warwick (1934), among others, included some bacteriological observations in their reports. Johnson and Meyer had only Gram-stained sections available for examination in the majority of their cases and were able to make cultures in only a few; thus, although bacteria were frequently found,

their complete identification was usually impossible. Hook and Katz, and Warwick reported only the results of examination of sections for bacteria. Hess-Thaysen (1914) reported bacteriological findings in a small number of his cases but had very few cultures. Cruickshank reported bacteriological findings in isolated cases in his series but did not attempt to carry out any extensive investigation. Browne gave the results of bacteriological examination in only a small number of his cases. The various authors who, as quoted above, reported an absence of bacteria in many cases of pneumonia in dead-born foetuses and infants who lived only a few hours, depended on examination of sections and reported no results of cultures.

From the meagre records available no accurate conclusions can be drawn as to the types of bacteria commonly associated with neonatal pneumonia. Hess-Thaysen (1914) found streptococci most often but did not specify their type; he never found pneumococci; coliform bacilli occurred in nearly all his cultures but he did not comment on the significance of their presence. Hook and Katz (1928) found streptococci, staphylococci, diplococci and Gram-negative rods. Johnson and Meyer (1925) also found staphylococci, streptococci and Gram-negative rods. Several authors have isolated pneumococci from cases of congenital lobar pneumonia (Netter (1889), Macdonald (1911) and

others quoted by Lauche (1927)); and Dodds (1928) recovered pneumococci along with staphylococcus aureus from her case of empyema. Apart from these cases records of proved pneumococcal infection in very young infants are scanty in the literature, and Ballantyne (1902) was of opinion that pneumococcal infections of the lungs were not common. Müller and Bayer (1934) endorsed this opinion. To judge by the lack of references in the literature, infection with B. influenzae (Pfeiffer) is rare in the neonatal period, though that organism is commonly associated with bronchopneumonia in older infants (Liston (1929)).

Browne (1921 and 1922) emphasised the frequent appearance of Bact. coli in his bacteriological investigations and advanced it as evidence of the importance of infection in the uterus or vagina in the production of neonatal pneumonia. These conclusions have often been quoted by later workers, but they were based upon a rather small number of cases and have been seriously criticised by Cruickshank (1930) on the ground that the great probability of post-mortem contamination with coliform bacilli, when the cultures were made at necropsy, was not sufficiently taken into account. So much was Cruickshank impressed with the liability of the body of the newborn baby to rapid post-mortem invasion by intestinal bacteria

that he was inclined to dismiss as unreliable nearly all reports that attributed a pathogenic role to the coliform bacilli, whether as a cause of general sepsis, of pneumonia or of meningitis, when such reports were based upon examinations carried out after death. The difficulty of interpreting the results of post-mortem bacteriological investigations is peculiarly acute in the case of newborn infants and is undoubtedly an important reason for the scantiness of present-day knowledge of the bacteriology of neonatal infections in general, and particularly of pneumonia, in which, owing to the uncertainty of clinical diagnosis and the difficulty of obtaining suitable material, bacteriological investigation during life is almost impossible.

PART II.

SCOPE AND METHOD OF INVESTIGATION.

INCIDENCE OF NEONATAL PNEUMONIA.

PATHOLOGICAL STUDY.

THE SCOPE AND METHOD OF THE INVESTIGATION.

This study is based upon the investigation of 177 cases, including 174 of pneumonia and 3 of bronchitis without pneumonia. These were found among 541 consecutive necropsies performed on infants up to 28 days old, including still-births, at four Edinburgh hospitals. The largest number came from the Royal Maternity and Simpson Memorial Hospital, most of the remainder from the Elsie Inglis Memorial Maternity Hospital, and a few from the Royal Hospital for Sick Children and the Obstetrical Unit of the Western General Hospital.

All the necropsies were performed either by the writer or by assistants working under her direction. All the bacteriological examinations were carried out personally by the writer except, in some instances, the making of the primary cultures at necropsy. All the histological examinations were made by the writer. In view of the known uncertainty of macroscopic diagnosis of neonatal pneumonia, every case of the 541 was regarded as a possible case of pneumonia and subjected to histological and, as often as was practicable, bacteriological examination, no matter how unlikely it might seem that pneumonia was present. Only by doing this was it possible to avoid missing the cases in which pneumonia was not obvious to the unaided eye, to

form a just estimate of its frequency and to obtain bacteriological results in the less severe cases. Histological examination was carried out in every case without exception. Bacteriological investigation was not always possible, but it was done in 474 cases, including 150 cases of pneumonia.

In carrying out the necropsy special attention was paid to any appearances in the lungs that might indicate the presence of pneumonia. Difficulty in macroscopic diagnosis arose in cases where the pneumonia was very slight and was associated with much atelectasis and oedema, usually in dead-born or very young live-born infants; or where massive pulmonary haemorrhage caused consolidation which concealed the presence of an accompanying pneumonia or simulated a pneumonia that did not exist. Apart from these circumstances, in most cases where pneumonia was present it was detected, or at least strongly suspected, at necropsy, and as experience was gained it became possible to detect many of the slighter cases even in the presence of much atelectasis. In many such the appearance of the lungs to the eye did not differ appreciably from that produced by atelectasis and congestion, but palpating fingers could distinguish an alteration in consistence, a slightly increased bulk and resistance, which could be recognised as characteristic. The condition of the pleural cavities and of the mucous mem-

brane of the respiratory passages, the contents of the trachea and bronchi and the character of any fluid that could be expressed from the lungs were noted. The necropsies were complete in all cases, excepting examination of the spinal cord, which was not done as a routine procedure. Full records of all pathological conditions or developmental abnormalities which might accompany pneumonia were thus obtained.

For histological examination pieces of tissue were taken from several parts of both lungs, including always any parts where macroscopic features suggested any suspicion of pneumonia. Histological sections were stained as a routine procedure with haematein and eosin and special staining methods (e.g. for fat, fibrin or bacteria) were employed when advisable in selected cases.

The bacteriological investigation included the examination of films and cultures from the lungs in all the 474 cases, whether pneumonia was suspected or not. In the first 250 necropsies, including 76 cases of pneumonia, cultures were made from the heart blood also, but in the later part of the investigation blood cultures were used only in selected cases, as it was found that, in dealing with post-mortem cases, the difficulty of interpreting the results was such that routine blood cultures were of little value.

In carrying out the bacteriological examination of the lungs, the pleural surface was seared, that part being selected in which there was most macroscopic evidence of pneumonia if such existed, or if not, the posterior surface of one of the lower lobes. Lung juice was withdrawn by means of a sterile capillary pipette and rubber teat, and was spread on horse-blood-agar in a Petri dish. At the same time films were prepared by spreading some of the lung juice on glass slides, to be stained by Gram's method. The culture plates were incubated aerobically; anaerobic cultures were not used except in selected cases. Subcultures were made on appropriate media for the isolation and identification of any bacteria that appeared on the primary cultures and were deemed to be of pathogenic significance. Streptococci were tested for haemolytic properties and, if non-haemolytic, for heat-resistance by exposure to a temperature of 60.C. for 15 minutes in a water-bath. Pneumococci were tested for bile-solubility and the power to ferment inulin, and were typed by the macroscopic agglutination method. Coliform bacilli were isolated on MacConkey's lactose-bile-salt-agar medium, and tested for type by appropriate fermentation and other biochemical tests. In addition, in every case in which pneumonia was found microscopically, sections of the lungs were stained by Gram's method and examined for

bacteria. This was found to be an important, even an essential, part of the investigation, as it showed not only the types of bacteria and the relative numbers of different types, but also their distribution in relation to the pneumonic areas.

Blood cultures were made by searing the surface of the right ventricle of the heart and withdrawing about 5 cc. of blood in a sterile capillary pipette. This was mixed with 50 cc. of nutrient broth in a glass bottle and incubated aerobically for 24 hours or longer, up to 7 days in the absence of growth, subcultures being made on horse-blood-agar, and resultant growths identified by appropriate means.

In every case the clinical record was examined. Consideration of the clinical features of pneumonia in the newborn is beyond the scope of this inquiry, but a knowledge of the facts of the maternal and obstetrical history is essential for a proper understanding of the pathological process and its causes, especially in the case of the youngest infants. The mother's health during pregnancy and the puerperium, the presentation, the duration of labour, the time of rupture of the membranes, the nature of delivery whether spontaneous or instrumental, the occurrence of complications or delay, the state of the child at birth, especially the presence and severity

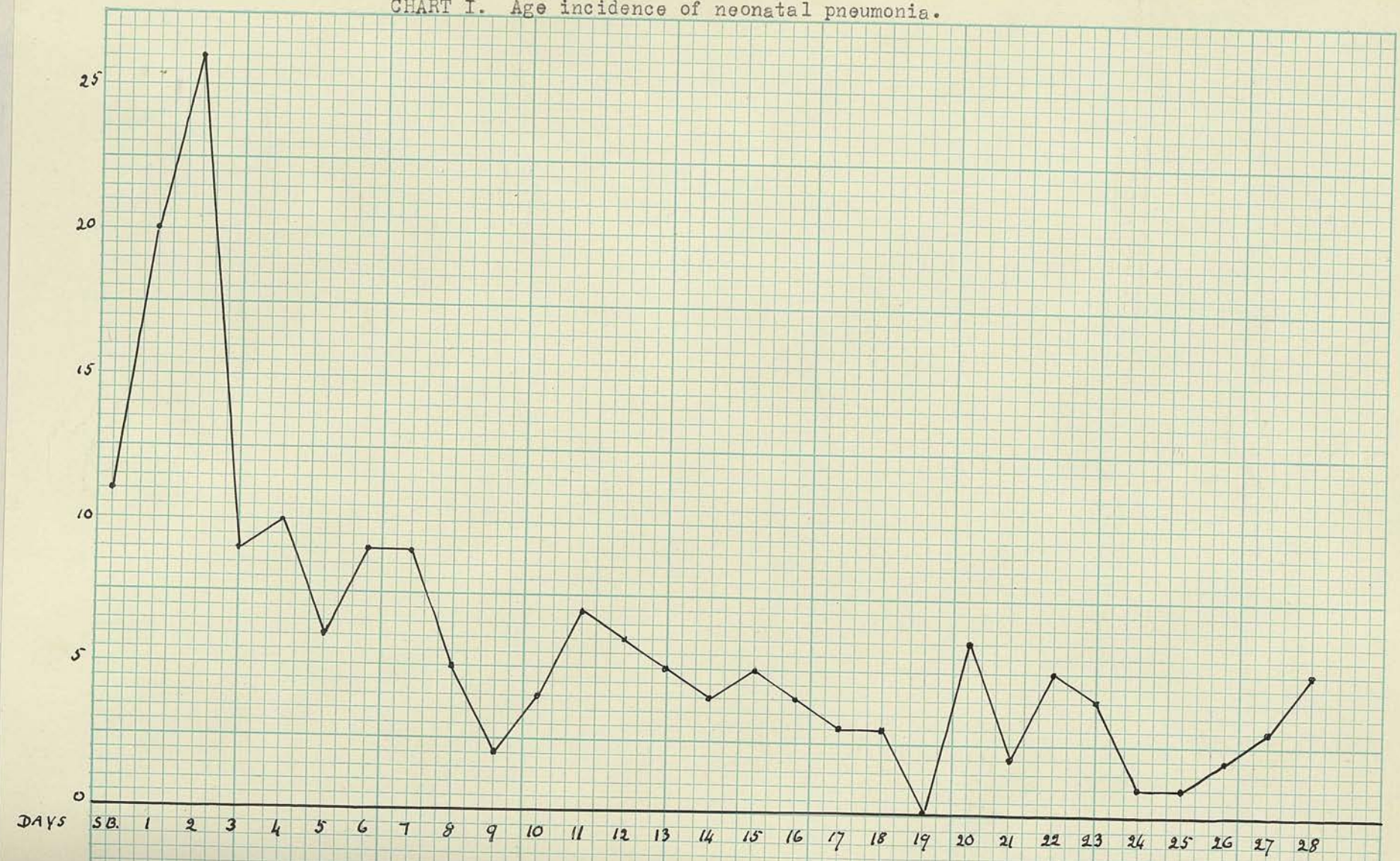
of asphyxia - all these may be important in connection with the development of neonatal pneumonia.

THE INCIDENCE OF NEONATAL PNEUMONIA.

The frequency of occurrence of neonatal pneumonia. The 541 infants who made up the whole series examined post-mortem included 93 who were born dead and 448 who were born alive and survived not more than 28 days. Among these there were 177 (32.7 per cent.) with inflammatory changes in the lungs, including 11 (11.8 per cent.) among the dead-born, and 166 (37 per cent.) among the live-born. This number included 3 cases in which the inflammatory changes were confined to the bronchi.

Pneumonia was not the cause of death in all these cases. A considerable number of the children had other lesions that might have proved fatal of themselves, and in some the pneumonia was of very small extent and probably less important than associated conditions. There were, however, many cases in which pneumonia was the sole and sufficient cause of death, and in all it must be regarded as at least

CHART I. Age incidence of neonatal pneumonia.



an important contributory factor.

Sex incidence. Among the 177 babies with inflammatory changes in the lungs there were 101 males and 76 females. This sex ratio did not differ significantly from that of the whole series of necropsies.

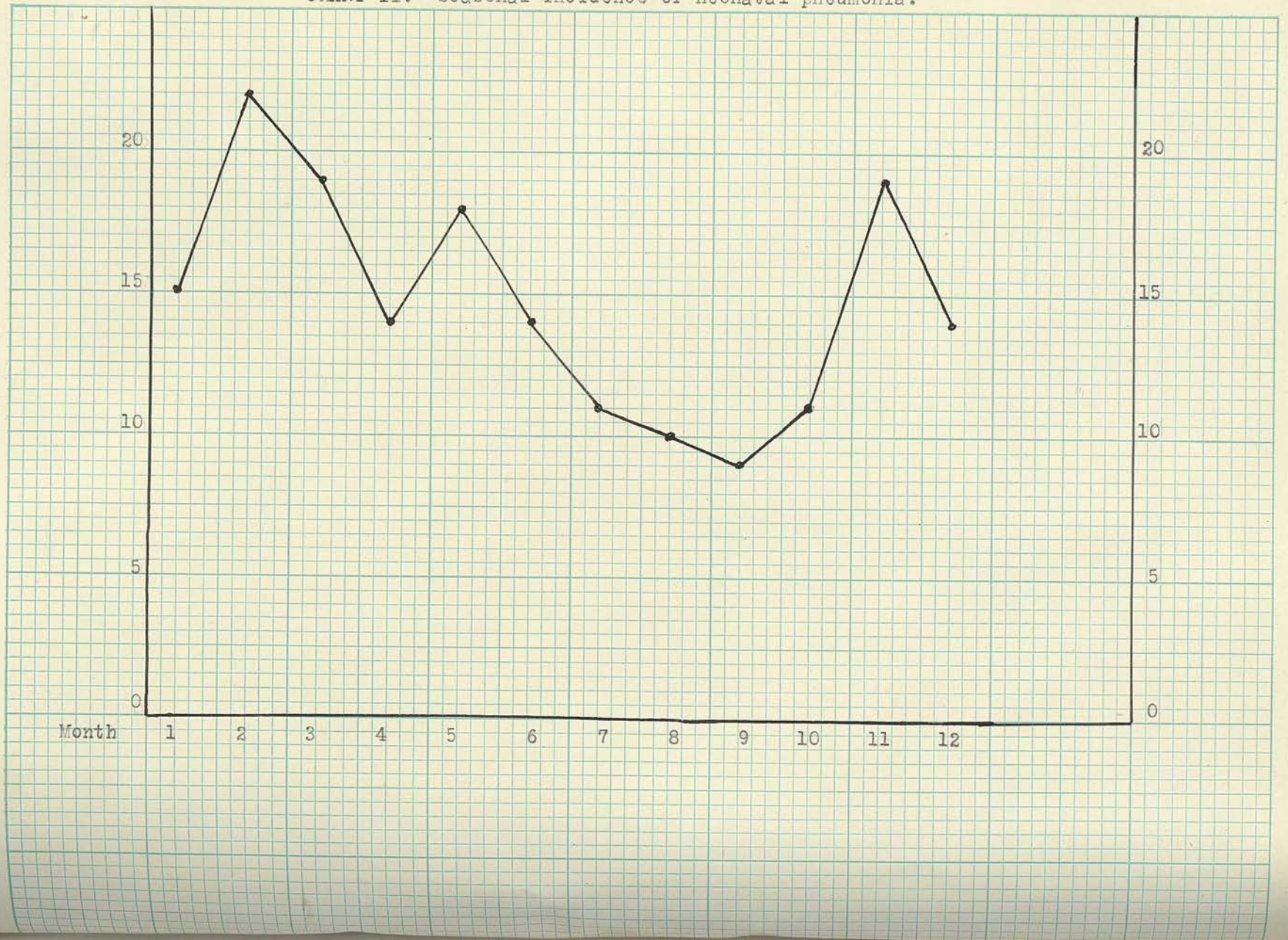
Age incidence. Chart 1 shows in graphic form the distribution of the pneumonia deaths throughout the 28 days of the neonatal period. Pneumonia occurred in 11 stillborn infants. Of the live-born infants with pneumonia 89 (53.6 per cent.) died in the first week of life; 33 (20 per cent.) in the second week; 23, (13.8 per cent.) in the third week; and 21 (12.6 per cent.) in the fourth week. Forty-six pneumonia deaths (27.7 per cent) occurred in the first two days, the largest number on any one day being 26 on the second. The large excess of deaths in the first week is thus accounted for to a great extent by the heavy mortality in the first two days, some of which is attributable to associated conditions rather than to the pneumonia itself. It was in this age group that the largest number of cases occurred in which the pneumonia was slight and some associated condition (notably intracranial haemorrhage) was the primary cause of death.

Maturity. In estimating the maturity of the infants the commonly accepted standard of 5½ lbs. birth weight was adopted, all who attained or exceeded that weight being classed as mature and all who fell below

it as premature. This method is not entirely satisfactory but probably gives more accurate results in practice than an attempt to estimate the actual period of gestation. According to this standard 100 of the 177 infants, including the stillborn, were mature, 77 premature. There was a greater excess of mature babies among those who died before delivery or on the first day of life than among those who survived longer: there were 8 mature to 3 premature among the stillborn, and 14 mature to 6 premature among those who died on the first day. This is accounted for by the greater frequency of serious intracranial haemorrhage among the larger babies. It is to be noted, however, that in proportion to the number of premature babies born an excessive number developed pneumonia. Premature babies may be estimated as about ten per cent. of all births. This figure is given by Browne (1922) and is in fairly close agreement with figures obtained from the Royal Maternity Hospital. Premature babies represented over 43 per cent. of all who developed pneumonia. The excessive susceptibility of premature babies to pneumonia has been noted by several authors (Cruickshank (1930), Johnson and Meyer (1925), Browne (1922)). Browne estimated that a premature baby is fourteen times more likely than a mature baby to develop pneumonia.

Seasonal incidence. As the investigation was

CHART II. Seasonal incidence of neonatal pneumonia.



carried on for four full years, it was possible to form some opinion as to the influence of season on the occurrence of neonatal pneumonia. Chart 2 shows the distribution of the cases among the twelve months of the year. During the years under review there was a decrease in the number of cases in the period from July to October as compared with the rest of the year, but otherwise the curve is somewhat irregular. The high figures for February and March are almost entirely due to the occurrence of an exceptionally large number of cases during those months in 1937. At that time influenza was very prevalent in the community, but the bacteriology of the neonatal cases did not suggest any direct connection with influenza in older people, except in a very few instances. The outbreak among the babies coincided with an unusual prevalence of premature births, for which influenza among the mothers appeared to be responsible. It might therefore be regarded as the result of an increase in the number of highly susceptible premature infants rather than as due to direct infection from adults affected with influenza.

PATHOLOGICAL STUDY.

Preliminary observations. In the study of neonatal pneumonia certain facts with regard to the condition of the lungs before and immediately after birth are of importance. In the unexpanded lungs of a foetus that has never breathed the lumina of the alveoli are small, the relaxed walls are thicker than after expansion has taken place, and the lining cells are a little more prominent. In microscopic sections the alveolar spaces are not entirely obliterated; the walls do not lie completely in apposition (Fig.1). There is considerable variation in the size of the spaces, even under apparently normal conditions. The undistended alveoli are occupied by a variable, though normally small, amount of fluid. Solid constituents of the liquor amnii are not ordinarily present, except in very small amount, so it is doubtful whether this fluid is liquor amnii or a transudate of lymph. In stained sections it leaves only a faint trace of albuminous deposit. The walls of the bronchi are contracted, the mucous membrane being thrown into folds, and the lumina of the smaller ones are nearly closed.

There is some doubt about the rapidity with which expansion of the lungs takes place after birth. The view that a healthy child who cries lustily at birth achieves immediate complete expansion is not

universally held. Henderson (1931) and von Reuss (1929), for example, believed that expansion takes place gradually and is not complete until some days after birth. The question is not easily settled by means of post-mortem studies. The undoubted fact that many infants who die during the first few days of life have incompletely expanded lungs does not mean that the same is true of healthy survivors. Indeed, it is not unusual to find the lungs of an infant who has lived less than an hour remarkably well expanded.

In the writer's opinion the lungs of a child who has lived even a few hours ought not to show gross atelectasis: the presence of areas of atelectasis large enough to be obvious on macroscopic examination would be regarded as abnormal. Possibly, however, it is not abnormal to find,on microscopic examination of such lungs, that air has not penetrated into every alveolus. Not infrequently, in the lungs of very young babies, well expanded alveoli are separated by solid bands, superficially resembling thick alveolar septa but actually composed of unexpanded alveoli which the air has failed to reach (Fig. 2). Macroscopically these lungs look well expanded and only slightly less voluminous than those in which expansion is complete; air is present in all parts and they float buoyantly in water. In the present study lungs in this condition are not described as atelectatic.

As actually seen in practice, in infants who have died before or soon after birth, primary or congenital atelectasis is often complicated by pathological changes produced by stress of birth. Chief among these are asphyxial congestion, often accompanied by haemorrhage into the coarse stroma or alveoli, and the presence of aspirated amniotic sac contents in excessive amount. Intra-alveolar haemorrhage and aspirated fluid produce a varying amount of expansion of the lungs, increasing their bulk and weight and altering their consistence. Neonatal pneumonia is often accompanied by these various conditions, which are peculiar to the lungs of the newborn and which complicate the pathological process and may influence its development and course. (Figs. 3, 4, 5, 15.)

Secondary atelectasis or collapse of the lungs must also be taken into account. It is apt to occur in the lungs of the newborn when obstruction to the entry of air develops as a result of the accumulation of mucus in the bronchi, of oedema or of pneumonia. In theory it can be distinguished from primary or congenital atelectasis by the fact that in the latter the lining cells of the alveoli retain their rounded or cuboidal shape, as in foetal lungs, whereas in secondary collapse they are flattened, as in expanded lungs. In practice this method of differentiation may be fallacious, as the lining cells not infrequently assume

a cuboidal shape in secondary collapse, especially after it has been present for some time. In secondary collapse, however, there is usually a demonstrable cause on which its extent and distribution can be shown to depend.

The significance of finding amniotic sac contents in the lungs of infants has been disputed. In the literature, difference of opinion is evident as to the amount of liquor amnii that normally enters the foetal lungs. Hochheim (1903) believed that liquor amnii fills the mouth and larynx of the foetus in utero and is drawn into the lungs with the first breath. Some workers (e.g. Ahlfeld (1888) and Leff (1936)) maintained that when the child is in utero the fluid fills the mouth and nasal cavities and passes down as far as the bifurcation of the trachea. Leff therefore considered that liquor amnii in the lungs of newborn infants is not an abnormal finding. Reifferscheid (1911), whose observations confirmed Ahlfeld's description of respiratory movements of the foetus in utero, considered that the fluid would not pass the closed glottis and would fill only the nasal cavity and mouth. Snyder and Rosenfeld (1937), who also obtained evidence of normal foetal respiratory movements both in animals and in the human subject, were strongly of opinion that the liquor amnii flows freely into the lungs of the foetus, enters the alveoli and, by afford-

ing a mechanism for dilatation of the air passages, aids in the structural differentiation of the lungs. They considered, however, that the presence of large quantities of solid amniotic debris is pathological, that it may cause bronchial obstruction and consequent atelectasis after birth, and that it depends on an abnormality of the liquor amnii and not on unusual respiratory activity on the part of the foetus. It seems possible, however, even if it be accepted that the foetus in utero is not normally in a state of apnoea, that the introduction of unusually large amounts of solid amniotic debris into the alveoli is the result of exaggerated respiratory efforts caused by asphyxia. That this is so is suggested by the fact that cases with excessive quantities of amniotic debris appear always to present other evidence of severe asphyxia, even in the stillborn, in whom obstruction to the entry of air could not be the cause of the asphyxia.

Farber and Sweet (1931) gave a review of the literature bearing on this question. Their conclusion was that the amount of amniotic sac contents in the lungs is a useful guide to the degree of foetal asphyxia. Helwig (1933) was in agreement with this. At present the prevalent view is that, while small amounts may be disregarded, any large quantity of amniotic fluid in the lungs after birth is an indication

of foetal asphyxia. When meconium is mixed with it, having been passed through a relaxed sphincter, it is evidence of still more severe asphyxia.

Classification. Classifications of neonatal pneumonia that have been suggested in the past have been based either on the method or on the supposed time of infection. The classification of Hess-Thaysen (1914) is an example of the first. As modified by Chase (1935) it is as follows:-

1. Metastatic infection:
   (a). Intra-uterine, through placenta;
   (b). Extra-uterine, e.g. from navel.
2. Aspiration, intra- or extra-uterine:
   (a). Products of conception;
   (b). Food or naso-pharyngeal material.
3. Bronchial or peribronchial infections without discoverable focus, extra-uterine.

The classification adopted by Johnson and Meyer (1925) had four groups, three of which depended on the supposed time of infection, thus:-

1. Antenatal infection: antenatal or intra-natal death.
2. Probable ante- or intra-natal infection: death usually within 3 days.
3. Pneumonia with hyaline membrane (type of asphyxia neonatorum).

4. Postnatal infection.

(In this classification Group 3 is obviously illogical; the cases included in it could have been placed in one of the other groups.)

Classifications of these types are satisfactory provided that the mode of infection is certain or the time of infection known. But when an attempt is made to fit any series of cases into either of them, difficulty is encountered with the large group in which the child survives more than a few hours (so that postnatal infection becomes possible), and dies within a few days (when infection before birth is still a possibility). This difficulty is not solved by drawing a line at the third day, as recommended by Hess-Thaysen, and classifying all cases of death before that time as examples of prenatal or intranatal infection, and all cases of longer survival as postnatal. Nor is it solved by assuming, as Kaldor (1933) did, that all cases associated with aspiration of liquor amnii are congenital. In the present state of our ignorance to make such assumptions is to sacrifice truth to convenience.

Therefore, in the study that follows, no aetiological classification is attempted. The following is an outline of the arrangement that has been adopted:-

1. Pneumonia associated with aspiration of contents of the amniotic sac or vagina:

(a). In the dead-born;

(b). In the live-born.

2. Pneumonia associated with other pulmonary conditions caused by stress of birth or otherwise peculiar to the newborn: atelectasis, haemorrhage, etc.

3. Bronchopneumonia and allied types.

4. Septicaemia with secondary (haematogenous) involvement of the lungs.

The cases are here divided into groups according to their distinctive pathological characters, which can be definitely ascertained, and not according to the time or mode of infection, on which matters certainty is often impossible. But an attempt is made to determine how far the pathological characters may serve to indicate the origin and pathogenesis of the disease. It will be shown that most of the cases in which infection was certainly or probably prenatal are included in Group 1, although not all the cases in that group can be so interpreted; that Group 2 contains many cases in which the time and method of infection were uncertain, though predisposing factors connected with birth were of primary importance; and that in the cases of which Group 3 is composed primary infection of the respiratory tract after birth was

almost certainly the cause.

GROUP 1. Pneumonia associated with aspiration of contents of the amniotic sac or vagina.

(a). In the dead-born. As it is only in the case of pneumonia in infants who are born dead that the prenatal origin of the pneumonia is beyond dispute, a study of this group will help to define the usual characters of 'congenital' pneumonia and make it more possible to recognise those cases in live-born infants that may legitimately be regarded as of the same type.

In the series there were 11 cases of pulmonary inflammation in dead-born infants, nine being cases of pneumonia and two showing inflammatory changes that were confined to the bronchi. In no case was there massive consolidation. Usually the pneumonia produced no recognisable alteration of the macroscopic appearance of the lungs, as compared with the unexpanded and congested lungs of an asphyxiated foetus, but in several instances, although pneumonia was not diagnosed at necropsy, the presence of an excess of liquor amnii or of aspirated meconium was recognised. In 4 cases pneumonia was suspected owing to the increased bulk and characteristic change in the consistence of the lungs. The lungs always showed the usual features of asphyxia - intense ven-

ous congestion with subpleural petechiae and sometimes small haemorrhages into the interlobular septa or lung substance. Other evidence of asphyxia was found elsewhere throughout the body, notably dilatation of the right side of the heart, subepicardial petechiae, turgidity of the large veins, and general venous congestion of the organs.

The microscopic picture varied according to the extent and severity of the pneumonia. A constant feature was evidence of excessive aspiration of amniotic sac contents into the lungs. Liquor amnii as such is not distinguishable microscopically from the fluid of pulmonary oedema, but its presence in the lungs is readily detectable by solid material in the fluid. Foremost among this are cornified squamous epithelial cells from the skin of the foetus (Fig. 4). They appear as scaly shreds of keratin or intact cells, usually without nuclei. In preparations stained with haematein and eosin they stain reddish or orange, or sometimes purplish. Often they are seen edge-on, when their sharp margins are evident. Lanugo hairs are also seen but less often than the cornified cells. Vernix caseosa is not uncommonly found. In sections stained with haematein and eosin it appears as amorphous masses which stain with eosin, lying free in the alveoli or bronchi, or adhering to their walls (Figs. 9-13). In sections suitably prepared these

masses can be shown to contain a large amount of fatty material and are thereby readily recognised as being composed of vernix caseosa. In live-born infants this material was sometimes found plastered against the walls of alveoli, alveolar ducts and bronchioles in the form of a continuous membrane (Fig.13). This appearance was not seen in any of the cases of still-birth. It is referred to again in the appropriate place. Sometimes meconium is found in the lungs, being recognisable by the presence of masses of bile-stained debris (Fig.5).

In the present study there was no case of pneumonia or bronchitis in a stillborn infant in which a considerable amount of amniotic sac contents was not found in the lungs. In 5 cases meconium was recognised either without or with the aid of the microscope.

The inflammatory exudate was cellular, the predominant cell type being the polymorphonuclear leucocyte (Figs.6,7,8). Fibrin was not found in any instance. In two cases the exudate was widespread, diffuse and uniform, but comparatively scanty, the alveoli not being completely filled and remaining unexpanded. In all the other cases the pneumonia was slight; two had exudate in the bronchi only without extension to the alveoli as far as the examination revealed. In the slight cases the exudate was usually

patchy and the distribution of the patches was erratic, without any traceable relation to the bronchi. It suggested in many instances that irritant material had been drawn straight into the alveoli, without lodging in the bronchi, which in consequence showed no inflammatory reaction. In this respect it differed from the distribution of the patches in true bronchopneumonia. Often the position of a patch apparently depended upon the presence of a deposit of amniotic debris or meconium (Fig. 7), but in nearly all cases the pneumonia was not co-extensive with the deposits of liquor amnii or meconium, many of which showed no admixture with inflammatory exudate.

The condition of the bronchi varied. As a rule the large bronchi were little affected, and in most of the slight and patchy cases even the smaller bronchi were practically healthy and were mostly unexpanded and empty. In other cases, however, they contained exudate mixed with amniotic debris or meconium (Fig. 8), and sometimes they were denuded of epithelium and showed more or less inflammatory damage to their walls. In cases that exhibited this more severe injury to the bronchi, pneumonic exudate sometimes occurred in alveoli nearly related to inflamed bronchioles, but the peribronchitis characteristic of true air-borne bronchopneumonia was not observed. Injury to the bronchi was usually more obvious when meconium had

been aspirated than when only liquor amnii was found, but this was not an invariable rule. In one of the cases with inflammatory changes in the bronchi only, meconium had entered the small bronchi but had not reached the alveoli.

Pneumonia was not the principal cause of death in most of these cases, if indeed it was in any. In 7 of the 11, lethal intracranial injury had been sustained. In the others, waterlogging of the lungs with liquor amnii, or blocking of the air passages with solid amniotic debris or meconium, or the results of severe asphyxia would probably have prevented the establishment of respiration even without the addition of pneumonia. Three of the babies were premature, eight were born at full term.

The obstetrical records of the cases showed that there was a forceps delivery in 3, breech delivery in 1, spontaneous delivery with vertex presentation in 7. There was one case of dry labour. Two mothers suffered from pre-eclamptic toxaemia during pregnancy; in one of these the placenta was noted to be 'unhealthy'; bacteriological examination of the foetus was inconclusive. Only in one case was a history obtained of any infective condition in the mother before parturition. This woman had a rigor before delivery and developed puerperal sepsis; her baby had aspirated a large amount of meconium and the

bacteriological result was negative.

A bacteriological investigation was carried out in 10 cases but a definite positive result was obtained in only one. In 6 cases cultures from the lung remained sterile and in direct films of lung juice and in Gram-stained sections of the lungs no bacteria could be found. In 3 cases the results were regarded as inconclusive: culture yielded a growth of coliform bacilli only, and organisms were not found in films and sections or, if found, were regarded as post-mortem invaders. In one case B. coli communior was obtained in pure culture from the lung, and in films and sections coliform bacilli were found not only to be present in large numbers in the pneumonic areas but to have been profusely phagocytosed by cells in the exudate; they were therefore regarded as almost certainly responsible for the pneumonia, which in this case was extensive and accompanied by bronchial injury. The delivery had been by forceps after a long dry labour. This was the only case of dry labour among the stillbirths.

Discussion of the observations on pneumonia in the dead-born. Pneumonia in this series of dead-born infants was invariably associated with aspiration of an excessive quantity of liquor amnii, with or without meconium. This was interpreted as a result of foetal asphyxia, of which other confirmatory evidence was

always present. This fact suggests that the occurrence of an inflammatory reaction in the lungs depended on the presence of aspirated material. The bacteriological investigation gave little ground for supposing that the irritant was necessarily bacterial. It is of interest that the only case in which there was definite evidence of bacterial infection in the child's lungs was the only one in which the history suggested the likelihood of infection of the amniotic sac as a result of a long dry labour. Six cases with negative bacteriological results and three others without acceptable evidence of bacterial infection suggested that the presence of bacteria is not necessary for the production of an inflammatory reaction; that is to say that the irritant may be chemical or mechanical, and present in the liquor amnii itself. It is not implied that the liquor amnii is always capable of producing an irritant effect; that is quite obviously not the case. But the evidence does suggest that at least in some cases the pneumonia may be due to irritating constituents of the liquor amnii. In five cases meconium was present in large amount; in others it may have been present in amount too small to be detected by macroscopic or histological methods. It was suggested by Helwig (1933) and by Warwick (1934) that the presence of bile salts may cause the liquor amnii to have an irritant effect on

the foetal lungs. This seems very probable and would explain certain of the present cases in which bacterial infection was apparently absent.

The fact that the aspirated material was almost always more extensively distributed in the lungs than the inflammatory reaction does not mean that the aspirated material was not itself the irritant. Aspiration would doubtless occur at different times during the course of labour, and material aspirated shortly before death would not have time to provoke an inflammatory response.

In conclusion, then, it may be said that, although the number of cases is not large enough to justify dogmatic conclusions, the evidence suggests that aspiration of amniotic sac contents is an almost constant, if not an essential, feature of pneumonia in the stillborn, and that in many cases the irritant is a non-bacterial one contained in the fluid itself. Bacterial infection of the foetal lungs may occur by aspiration and is most probable in cases of long dry labour following premature rupture of the membranes. In all cases foetal asphyxia, which induces premature or excessive respiratory efforts on the part of the foetus while it is still within the uterus or vagina, is an important and probably a necessary factor.

(b). In the live-born. In 33 cases of pneumonia in live-born infants there was evidence of aspiration of contents of the amniotic sac or genital canal.

(i). With excessive aspiration of amniotic sac contents. There were 30 live-born infants in whom pneumonia was accompanied by aspirated amniotic sac contents in excessive amount. They all died within 4 days after birth, and all but 3 in the first 2 days. In most of them the pneumonia had the same characters as in the dead-born babies already described. In most cases it was slight and had produced no massive consolidation of the lungs. The exudate occurred either in small patches which usually had no relation to bronchi, or in a diffuse and widespread distribution but scanty in amount, not completely filling the alveoli. The bronchi usually showed little inflammatory change. In 5 cases the pneumonia, though of the same histological type, was more severe and had produced fairly extensive consolidation. Frequently the pneumonic patches were at the site of deposits of amniotic debris, but, as in the dead-born infants, deposits of liquor amnii might be found in which no inflammatory reaction had arisen, while sometimes the pneumonia was more widely distributed than the aspirated material, especially in those who survived till the second day or longer and in whom the

pneumonia was fairly severe.

Among these cases were 11 which showed the condition described by Johnson and Meyer (1925) as 'hyaline membrane', and by Farber and Sweet (1931) and Farber and Wilson (1932) as 'vernix membrane'. This remarkable structure consists of homogeneous material, staining strongly with eosin and having a somewhat hyaline appearance, which lines the bronchioles, alveolar ducts and alveoli with a thick, more or less continuous layer closely applied to the walls (Figs.12,13).It is not invariably accompanied by pneumonia; it occurs quite often without any inflammatory reaction (Fig.11), and in cases with pneumonia it may be more widespread than the exudate. Johnson and Meyer (1925), who described it as resembling the 'hyaline membrane' of influenzal pneumonia, believed that it was probably formed of vernix caseosa, finding that it was always loaded with fat. Farber and Sweet (1931) and Farber and Wilson (1932) had no doubt about its composition, and named it 'vernix membrane', thereby separating it definitely from 'hyaline membranes' of inflammatory origin. Steinharter (1937), however, described a case in which the membrane contained no fat, and concluded that not only vernix but viscous fluid, either liquor amnii or true oedema, might in some circumstances give origin to the membrane.

In this study, in every example to which fat stains were applied, the membrane was loaded with fat. Further, material of similar appearance but in the form of masses lying free in the air spaces (Fig. 9) was frequently found to contain a large amount of fat. As Farber and Wilson (1932) pointed out, this represents the preliminary stage of membrane formation, before the material is plastered against the walls by inspiratory effort or artificial respiration (Fig. 11). In the writer's opinion this material is vernix caseosa in most cases, though possibly not in all. The term 'vernix membrane' will therefore be used in preference to the ambiguous term 'hyaline membrane'.

All the babies in whose lungs vernix membrane was found were badly asphyxiated at birth and failed to breathe well. Their ages at death ranged from 3 hours to 4 days, but only two survived the second day. Except in the oldest child, who had a very massive pneumonia, the lungs always showed more than usually severe atelectasis. Sometimes the terminal bronchioles were acutely over-distended, while no air had reached the alveoli related to them, which were in consequence completely unexpanded (Fig. 14). In several cases the small areas that had been aerated showed acute vesicular and interstitial emphysema, with air bullae in the interlobular septa and projecting under the pleura, a

condition seldom seen in newborn infants in the absence of vernix membrane, unless it is caused by over-vigorous application of artificial respiration. This combination of atelectasis and over-distension indicates that the vernix membrane offers a serious obstruction to the passage of air to and from the alveoli, as indeed is obvious from the nature of the condition as seen under the microscope.

In all cases with vernix membrane except one the pneumonia was of the type already described: a diffuse but usually scanty exudate, or patches with an erratic distribution, without much inflammatory change in the bronchi, apart from the presence of exudate. The one exception, in a child who lived two days, was a fairly extensive diffuse pneumonia with severe bronchial inflammation, from which B. influenzae was isolated in pure culture.

One case in the group with aspirated amniotic sac contents had entirely different pathological characters. The child lived 32 hours. There was massive consolidation at the bases of the lungs, much of which was due to haemorrhage, and throughout the solid parts suppuration had begun in the bronchi and in many small patches of alveolar tissue. Immense numbers of staphylococci were present throughout the affected parts, often mixed with masses of amniotic debris, and staphylococcus aureus was isolated in pure cul-

ture from the lung. The appearance suggested that a large quantity of heavily infected fluid had been drawn into the lungs. It was noted in the history that the liquor amnii was foetid, so the source of the infection was reasonably clear.

(ii). With aspiration of infected mucus, probably from the vagina. In addition to the 30 cases in which excessive aspiration of amniotic sac contents was obvious, there were 3, in children aged 12, 20 and 29 hours, in which, without recognisable amniotic debris, the bronchi were filled with masses of mucus which contained remarkable numbers of bacteria, and a severe inflammatory reaction had been set up, beginning in the bronchi where serious damage to the walls was evident, and spreading to neighbouring alveoli which were extensively consolidated.

It seemed probable that the heavily infected material in the bronchi had been aspirated, most likely from the vagina during birth. The bacteria found in films and sections, and obtained in culture, were streptococcus viridans in one case, Bact. coli in one, and non-haemolytic streptococci along with Bact. coli in one. In one case there was a breech delivery, in one a forceps delivery with face presentation, in one a spontaneous delivery with vertex presentation but the child was asphyxiated at birth. In all these cases therefore premature respiratory efforts on the part of

the foetus were probable and might have caused aspiration of bacteria-laden mucus from the birth canal.

Many of these babies had lesions additional to the pneumonia which were probably more important than the pneumonia as cause of death. Seven had severe intracranial haemorrhage; two had serious alimentary haemorrhage and two intraperitoneal haemorrhage; three had gross developmental defects; one died of meningitis. The clinical records of the majority indicated severe asphyxia at birth and evidence of this was found post-mortem in all cases. Eighteen of the babies were mature, fifteen premature.

The obstetrical records of most of these cases were unremarkable. There were 2 cases of Caesarian section, 3 breech presentations, 6 forceps deliveries (2 in breech cases), 2 dry labours. In the remainder labour was normal and delivery spontaneous. Except in the case of staphylococcal infection already mentioned, in which the waters were foetid, and one other in which, following a dry labour, the placenta was noted to be 'unhealthy', there was no evidence in the records of infection in the genital tract before parturition. Two mothers had pyelitis and other two suffered from toxaemia of pregnancy. The rest were healthy.

Bacteriological investigations were carried out in 26 of the 33 cases in which there was clear evidence of aspiration before birth. In 3 cases (in

children aged 1 hour, 5 hours and 13 hours) the result was negative. In 9 cases the result was regarded as inconclusive, either because organisms obtained in culture were not found in films or sections, or because organisms seen in films and sections and obtained in culture were of types that commonly occur as post-mortem invaders (notably the coliform bacilli) and the evidence of their being anything more than that was regarded as insufficient. Among the 14 cases in which a positive result was obtained, 1 was a pure infection with B. influenzae and 1 with staphylococcus aureus; the infecting organisms in the remaining cases were green-producing streptococci, indifferent streptococci and coliform bacilli, alone or in combination. All the negative and inconclusive results were in cases in which the pneumonia was slight. Bacteria were always found when there was massive consolidation.

Discussion of the observations on pneumonia in live-born infants associated with prenatal aspiration is deferred until after consideration of the next group of cases.

GROUP 2. Pneumonia associated with other pulmonary conditions caused by stress of birth or otherwise peculiar to the newborn.

(a). Pneumonia with atelectasis. Lungs in

which aspirated amniotic sac contents were found always showed more or less severe congestion and atelectasis as well as a water-logged condition due to the aspirated fluid. There were other cases in which the state of the lungs was similar and in which the pneumonia assumed the same characters but in which no clear evidence of aspiration was found. There were 20 such cases and they all had certain features in common. The lungs were very poorly expanded, congested and oedematous. The pneumonia was, in most cases, not very extensive, though in a few it had produced fairly massive consolidation. It had the same pathological characters as in the cases with aspirated liquor amnii - a diffuse, usually scanty exudate, or patches without clear relation to bronchi, and an absence of severe inflammatory changes in the bronchi. Practically all the children had exhibited conditions that might explain the persistence of atelectasis: most of them were severely asphyxiated or feeble at birth; 8 had intracranial haemorrhage; all who presented no other reason for persistent atelectasis were premature and puny. Seventeen of them died in the first week; the oldest was 17 days and had intracranial haemorrhage.

The obstetrical histories of this group revealed 1 case of Caesarian section, 2 forceps deliveries, of which one was by the breech, 2 dry labours

and 1 case of hydramnios. Five mothers had pre-eclamptic toxaemia of pregnancy; none showed any infective condition.

Bacteriological examinations were made in 16 of these cases but 6 gave inconclusive results. Of the 10 in which results were obtained, 2 yielded haemolytic streptococci and 4 viridans type or indifferent streptococci; 3 gave Bact. coli, and 1 the bacillus of Friedländer.

(b). Pneumonia with massive pulmonary haemorrhage. In the groups already considered, and in those to be considered in later sections, some amount of haemorrhage, often large, was a common occurrence in association with pneumonia, depending either upon the intensity of the inflammatory reaction or upon accompanying asphyxial congestion. In the group now to be considered haemorrhage appeared to be the primary event, the inflammatory reaction developing secondarily in areas of tissue devitalised by haemorrhage.

Gross pulmonary haemorrhage is not uncommon in the newborn and may be a cause of death, usually in the first two or three days of life. It may be so severe and extensive that practically the whole of both lungs is massively consolidated by it (Fig. 37), the alveoli being filled to capacity with blood (Fig. 15); or it may affect localised areas of

greater or less extent, often having a distribution macroscopically resembling bronchopneumonia and readily mistaken for it. The cause is obscure. This condition is probably the 'acute haemorrhagic pneumonia' which Browne (1921 and 1922) believed to be the first stage of an intense inflammation. Ylppö (1919) ascribed it to bacterial action. Cruickshank (1930) attributed it as a rule to asphyxia, but noted that many babies in whom it occurred were born of toxaemic mothers.

Massive pulmonary haemorrhage was met with many times in the course of this investigation, sometimes associated with infective conditions, for example in cases of meningitis or septicaemia, but more often without any evidence of an infective element in the case. Usually it was not accompanied by an inflammatory reaction in the lungs, and when that was so bacteriological examinations of the lungs invariably gave negative or inconclusive results. Sometimes it occurred, accompanied by haemorrhages elsewhere, as a manifestation of 'haemorrhagic disease of the newborn'. Some cases could be explained by birth asphyxia, but not uncommonly it occurred in infants two or more days old, whose condition at and for a time after birth was thought to be satisfactory. Some of these had mothers who had suffered from toxaemia. In no case was there evidence of embolism. The cause of the condition can-

not at present be adequately explained, but in the writer's opinion in most cases it is not an inflammatory condition and its cause is not bacterial.

When massive haemorrhage occurs it may cause devitalisation of the lung tissue in the affected area by occasioning an arrest or impairment of the circulation. In these circumstances, as might well be expected, bacterial infection sometimes gains access to the devitalised area and sets up an inflammatory reaction. This inflammatory reaction, in the present series, was always of comparatively slight extent and confined to small areas of necrotic tissue among haemorrhage which was much more widespread. This type of pulmonary haemorrhage is itself a fatal condition and survival can seldom be long enough, in severe cases, to allow time for the subsequent infection to advance far. (Fig. 16)

There were 13 examples of this lesion. Nine of the babies died in the first week, 7 in the first three days. The youngest was 24 hours old, the oldest was 20 days. Seven of the babies were premature. In four cases in the younger babies there was severe asphyxia at birth. The pneumonia was probably never the primary cause of death or more than a minor contributory factor. The pulmonary haemorrhage was more important and was often itself the principal cause of death, though in some cases other lesions of a lethal

character were present. Seven of the children had intracranial haemorrhage, most often subarachnoid or intra-ventricular, not associated with tears of the dural septa. One child had multiple haemorrhages. One had a grave congenital cardiac defect. In only one case was there evidence of an infective condition apart from the lungs - acute peritonitis in a child who lived 5 days.

The obstetrical records of this group showed that there were 4 cases of breech presentation but no instrumental deliveries. Two of the mothers had suffered from pre-eclamptic toxaemia during pregnancy. In the remaining cases there was no record of any abnormality.

Bacteriological investigation was made in 9 cases. The results were negative in 2 cases and inconclusive in 4. Three cases yielded non-haemolytic streptococci, accompanied by coliform bacilli in 2. The small number of satisfactory bacteriological examinations is probably due to the fact that the pneumonia was rarely detectable macroscopically in the midst of the massive consolidation caused by haemorrhage, and consequently the material obtained for bacteriological purposes may often have been taken from an area of pure haemorrhage and so did not give a true result.

Discussion of the observations on pneumonia in the live-born associated with prenatal aspiration and other conditions peculiar to the newborn. These two groups of cases may be considered together because they had many points of similarity. Those with prenatal aspiration and those with atelectasis had in common deficient expansion and aeration, congestion and a water-logged condition of the lungs. In both these groups the pneumonia had the special characters described and closely resembled that found in the stillborn infants. Although its characters suggested that it was caused by an irritant that entered the lungs by the respiratory tract, it was not a typical bronchopneumonia; it showed less severe inflammatory injury to the bronchi and its distribution bore a less strict relation to the branches of the bronchial tree, being more erratic in the slighter patchy cases, and more diffuse and uniform in those of wider extent.

As these special characters were found no less in cases that provided no evidence of prenatal aspiration than in those in which aspiration had certainly occurred, it would appear that they depend less on the actual mode of infection (aspirated or air-borne) than on the state of the lungs in which the inflammatory reaction develops, especially on the presence of atelectasis and oedema.

If this be accepted, the problem of determining the mode and time of infection is more than ever difficult. As cases of this type occur at and after the end of the first week, they cannot all be regarded as 'congenital' and due to infection received before delivery. Even those with aspiration cannot all be so regarded. Those in the first few days may be assumed to have begun before birth and, like those in the stillborn, may be due to irritant elements in the aspirated material rather than to bacterial action. In such cases, lacking superadded bacterial infection, the pneumonia would probably not develop into massive consolidation. It is significant that all severe cases in the group showed bacteria. Many slighter cases, however, also showed bacteria, and when this occurred in children 2 or more days old and, as often happened, the pneumonic areas corresponded to the position of bacteria and not to the position of aspirated masses, it must be inferred that the pneumonia was due to bacterial action and was probably of postnatal origin.

Only a few cases showed clear pathological evidence of prenatal or intra-natal bacterial infection or a probable source of that infection in the history. Reference has already been made to them; they showed much more definite evidence of septic aspiration than any of the other cases.

A comparison of the bacteriological results of the cases of pneumonia in the stillborn and in the live-born, considered along with the obstetrical records and other available evidence, suggests that, except in individual cases, bacterial infection acquired before birth is not of great importance, although when it does occur it has disastrous consequences for the child; but that the conditions produced in the lungs by aspiration, or by persistent atelectasis with accompanying congestion and oedema, are most favourable to bacterial invasion after birth.

In the case of pneumonia with massive pulmonary haemorrhage, the introduction of bacterial infection is regarded as secondary and accidental, and probably occurs usually after birth. There was no direct evidence of aspiration during birth in any of the cases, although the two youngest babies, who both died at 24 hours, and two others were delivered by the breech, which is supposed to favour aspiration. As the inflammatory reaction was at a very early stage in all cases, even in the youngest postnatal infection was possible.

GROUP 3. Bronchopneumonia and allied types (postnatal respiratory tract infections).

(a). Pneumonia with evidence of septic aspiration after birth. There was a small group of cases in which features of the pathological picture and history indicated that pulmonary infection had arisen as the result of aspiration of food or vomited matter into the lungs. There were 8 of these, the ages ranging from 3 to 16 days. With one exception - a premature baby aged 12 days with intracranial haemorrhage, in whose case aspiration had probably occurred only a short time before death and the pneumonia was at an early stage - consolidation was extensive in all cases and the lung lesion of a grave type. It was characterised by masses of foreign material which was found at necropsy in the air passages and recognised to be the same as the stomach contents. In one case it was thick white milk curd; in six cases it was more or less bile-stained fluid gastric contents; in one case it was mostly meconium. In this last case the child developed, soon after birth, symptoms of acute intestinal obstruction, with vomiting of meconium. Operation revealed a volvulus. The child died on the fourth day. Meconium was found in the bronchi and lungs at necropsy, and microscopically was seen to have entered the finer bronchi and alveoli.

In all cases in this group on microscopic ex-

amination the presence of aspirated material was obvious in the bronchi and sometimes in the alveoli also. In every case it was exceedingly heavily infected with bacteria. In the 7 advanced cases the walls of the bronchi were badly damaged by purulent inflammation, and suppuration threatened or had developed around the bronchi and in areas of alveolar substance. Extensive haemorrhage was a feature of these cases, and in the haemorrhagic areas much of the blood was lysed and the lung tissue showed necrotic changes and appeared to be undergoing digestion (Fig. 17). No doubt this appearance was exaggerated by post-mortem changes, but its occurrence evidently depended on the presence of gastric secretion in the parts; and that the aspiration was not merely a terminal event was proved by the severity of the inflammatory reaction that had developed. In the slighter case referred to above, in which milk curd was found in the air passages, inflammation had developed in the bronchi but had only begun to spread to the alveoli at the time of death.

Three children in this group, in addition to the one, already mentioned, who had intestinal obstruction, had a history of vomiting. The records of the remaining four contained no reference to vomiting; two had intracranial haemorrhage, and one had thrombosis of the renal veins with infarction of the

kidneys. The maternal and obstetrical histories contained nothing relevant.

Bacteriological examinations were carried out with cultures in 5 cases, and in the other 3 Gram-stained sections of the lungs were examined but no cultures were made. In every case sections showed immense numbers of various bacteria in the aspirated material and in affected parts of the lungs, coliform bacilli preponderating. Cultures in 5 cases yielded profuse growths of coliform bacilli, accompanied in 3 cases by a variety of other organisms.

Pneumonia caused by aspiration of vomited material is not confined to the neonatal period but it appears to be of more frequent occurrence in newborn babies than in older infants and children. This is probably to be explained by the greater tendency of very young babies to regurgitate gastric contents, and to the risk that this may enter the trachea if regurgitation occurs when the child is lying in an unsuitable position, e.g. on its back, and is unable to change its position. It is not necessary to postulate any inefficiency of the laryngeal reflex at this early period of life.

(b). '<u>Typical' bronchopneumonia</u>. Most of the types of pneumonia considered in the foregoing sections - for example, that caused by aspiration and

that developing in atelectatic lungs - are forms of bronchopneumonia, but in some respects atypical because of the mode of infection or the conditions obtaining in the affected lungs. The cases now to be considered were different in certain particulars and bore a closer resemblance to bronchopneumonia as it is commonly met with in older infants and children as a result of air-borne infection. It is necessary therefore at this stage to define what is meant by 'typical' bronchopneumonia.

In a study of pneumonia in childhood McNeil, Macgregor and Alexander (1929) gave a detailed description of the pathological changes in the lungs in bronchopneumonia and emphasized certain features of the process which they regarded as distinctive and essential. Chief among these they considered bronchitis: the inflammatory process begins in the bronchi and spreads from them to the alveoli. The inflammation of the bronchi is much more than a superficial catarrh of the mucous membrane; it is an intense inflammation which involves the whole wall and its lymphatic plexus. The bronchial wall therefore shows, in addition to catarrh, an interstitial inflammation, indicated by swelling and inflammatory cell infiltration, which varies in severity in different cases but is always present to some extent. The spread of the inflammation to the alveoli is in part a direct

bronchial spread along the lumen of the bronchi to their terminal expansions, and in part peri-bronchial, through the thickness of the wall to immediately adjacent alveoli which are not in communication with the lumen of the bronchus. It is therefore usual not only to find the terminal bronchioles forming the centres of pneumonic patches, but also larger bronchi, cut at some distance from their terminations, surrounded by a ring of consolidated alveoli. This is the result of the interstitial inflammation and lymphangitis which these workers regarded as 'a constant feature of all forms of true bronchopneumonia and - - - of the very essence of the pathological process'. Even when bronchopneumonia assumes a massively confluent form its essential character and method of extension remain apparent from the greater density of exudate in the alveoli closely related to bronchi and bronchioles, and by the severity of the bronchitis with interstitial inflammation and lymphangitis.

Holt and McIntosh (1933) were in agreement with these authors in regarding interstitial inflammation as an essential feature of true bronchopneumonia. Chase (1935) also noted the peri-bronchial distribution of the exudate, indicating lymphogenous infection, and regarded it as an important point of distinction between cases in which pneumonia in the

newborn followed extra-uterine upper respiratory tract infection (i.e. true or typical bronchopneumonia) and those in which it was caused by direct aspiration.

In the selection of cases for inclusion in the group of 'typical' bronchopneumonia the features that were regarded as essential were:- (1) bronchitis severe enough to produce not merely superficial catarrh but some amount of interstitial inflammation in the substance of the bronchial wall; (2) a strictly bronchial and peri-bronchial distribution of the pneumonic areas; and (3) absence of evidence of aspiration of foreign material into the lungs.

Fifty-five cases in the series fulfilled these criteria. This was therefore the largest pathological group. The children's ages ranged from 30 hours to 28 days. Only four were under 4 days old, after which age cases were more frequent and were fairly uniformly distributed throughout the month. It appears from this that cases of typical bronchopneumonia form only a very small proportion of all cases in the first three days of life, are more common not only relatively but absolutely from the fourth day onward, and constitute the majority of all cases during the second half of the month.

Most of these cases showed consolidation that was moderately or very extensive. In all but a very

few both lungs were affected, though not often to an equal extent. In most cases of even moderate severity some amount of confluence of the pneumonic patches had occurred; in the more severe it was usually very extensive, often involving a whole lobe or more in one or both lungs. Confluence was most often of greatest extent in the lower lobes but was not uncommon in the posterior part of the upper lobes. Pneumonic areas were usually deep red and firm, the aerated lung substance also being intensely congested. When there was extensive confluence, the consolidated areas on section were often fairly uniform in colour but rarely quite uniform in consistence; the cut surface was moist, and opaque greyish or blood-stained fluid could be expressed from it, and mucopus, rarely very thick, from the cut ends of the bronchi. Sometimes the appearance was indistinguishable from that of massive pulmonary haemorrhage, but apart from this the macroscopic diagnosis of pneumonia seldom presented difficulty, except in the slightest cases. Atelectasis, probably as a rule secondary collapse, was usually present but seldom extreme.

Microscopic examination showed that the exudate was cellular, containing polymorphonuclear leucocytes as the predominant cell (Fig. 20), and varying numbers of histiocytic macrophages and desquamated alveolar lining cells. When the exudate was abundant

it often contained a large number of granulocytes with unsegmented nuclei, i.e. at the meta-myelocyte stage of development. Fibrin was absent, or present only in exceedingly small amount. Oedema was often considerable, and haemorrhage was common and often contributed greatly to the consolidation, being sometimes responsible for wide confluence when the cellular exudate was confined to the immediate vicinity of bronchi. Alveoli that were not completely filled with exudate or blood were often collapsed. Bronchi that formed the centres of consolidated areas were denuded of epithelium and filled with inflammatory exudate; their walls showed cellular infiltration and swelling of varying degrees of severity (Figs. 18,19). These changes usually affected the smaller bronchi more than the larger, which sometimes escaped serious injury. In three cases suppuration had occurred, originating in severely inflamed bronchi. Pleurisy was rare, being found in only three cases, two of those with suppuration and one other, in which septicaemia originating in the lungs had produced a polyserositis which affected all the serous sacs.

Although in essentials these cases resembled typical bronchopneumonia as it is seen in older infants and children, in detail there were differences. The absence or scarcity of fibrin in the exudate contrasted with its not uncommon abundance in older

subjects, especially where there is confluence. Confluence, when present, was due to the widespread distribution of cellular exudate, or in part to oedema in the parts furthest from the bronchi, or to haemorrhage. Massive haemorrhage was much commoner in the neonatal cases than in older children, and often obscured the peri-bronchial mottling that is so characteristic a feature of confluent bronchopneumonia. Interstitial inflammation of the bronchial walls and framework of the lungs, though always present, was not as severe as it often is in older infants. The probable reason for this is the short duration of pneumonia in the newborn. Although interstitial inflammation and lymphangitis occur at the earliest stage of bronchopneumonia, the process is progressive and is seen in the most severe form in cases of long duration. Such cases do not occur in the newborn. The unreliability of clinical diagnosis makes it impossible to know for how long before death a newborn baby has had pneumonia. The pathological picture, even in severe cases, suggested an inflammatory process that had developed rapidly rather than one that had been long in existence. It is probable that few infants in the neonatal period survive the onset of pneumonia for more than a few days. The interstitial inflammatory changes resembled in extent and severity those found in rapidly fatal cases of bronchopneumonia

in older infants. The bronchi contained mucopus which was often blood-stained but was seldom thick yellow pus such as is found in many cases of bronchopneumonia in older children. This difference also is accounted for by the short duration of the disease. The disseminated type of bronchopneumonia, in which all the patches are small and discrete without any confluence, was rarely seen; in this series it occurred only in babies nearing the end of the first month of life.

In this group 25 of the babies were premature, 30 were mature. Eight had intracranial haemorrhage, one alimentary haemorrhage, and two thrombosis of the renal veins. Three had grave developmental defects of the heart, and one had congenital hypertrophic stenosis of the pylorus. One had umbilical sepsis without evidence of septicaemia. Four had clinical symptoms of gastro-enteritis. Four died of meningitis not proved bacteriologically to be connected with the pneumonia, which was at a very early stage. One developed polyserositis as a complication of pneumonia. A considerable number had stomatitis, which was very severe in two cases.

The maternal and obstetrical histories showed that there were 8 forceps deliveries, mostly in cases in which the infants survived into the third week; 5 breech deliveries; 1 dry labour in the case of a child who lived 28 days. One child who died at 2 days

was delivered in an intact amniotic sac, the second of twins of whom the first remained healthy. Four mothers had toxaemia of pregnancy; two had pyelitis; two had leucorrhoea.

Bacteriological examinations were carried out in 47 cases. The result was inconclusive in 9 cases; 38 gave positive results. Pneumococci were isolated from 6 cases, always accompanied by other organisms, most often B. influenzae and occasionally streptococcus haemolyticus and Gram-negative cocci of the Neisseria group. Streptococcus haemolyticus occurred in 5 cases, alone in 3; viridans type streptococci in 2; indifferent streptococci in 9, usually in association with other organisms. B. influenzae occurred 8 times, alone once, accompanied by other organisms in 7 cases. Coliform bacilli were isolated from 16 cases, 9 times alone, 7 times in association with other organisms. In a few cases a great variety of bacterial species was present, many of which could not be identified.

Discussion of the observations on typical bronchopneumonia. The cases in this group may be regarded as representing the common form of pneumonia in the newborn that results from postnatal air-borne infection. That this was their mode of origin is suggested by their resemblance to cases known to be so caused in older infants, and by the age incidence of

the type in the present series. It is true that in the youngest infants in the group birth infection was possible though without evidence either from the pathological study or from the clinical history; but even in the case of the youngest, who died of intracranial haemorrhage, it is not impossible that the early pneumonia that was found might have developed entirely within the 30 hours of postnatal life. No well developed case was seen before the fourth day, by which time postnatal infection must be considered the greater probability. For reasons that will be given in a later section, the writer is not of opinion that the frequency of infections with coliform bacilli means a corresponding frequency of infection acquired before delivery.

(c). Bronchitis without pneumonia. Only one child in the series who was born alive showed bronchitis without any spread of the inflammatory process to the alveoli. This was a premature infant who died on the 23rd day with a severe stomatitis and pharyngitis. Streptococcus haemolyticus was isolated in pure culture from the lungs.

(d). Hypostatic pneumonia. In two infants, aged 10 days and 14 days, both extremely feeble premature babies, the pneumonia had the typical features

of a terminal hypostatic pneumonia. The consolidation, which was of an indefinite character and accompanied by much oedema, was confined to the bases and posterior borders of the lungs.

Bacteriological examination was carried out in one of the cases and a non-lactose-fermenting coliform bacillus of the Bact. coli group was isolated.

(e). Staphylococcal pneumonia. Pneumonia due to infection with staphylococci (other than haematogenous infection) is indubitably a type of bronchopneumonia but, as seen in the course of this study, it had features so constant and so distinctive that it is convenient to place such cases in a group by themselves for separate description.

Staphylococcal pneumonia has been described by several observers in the past. Cases that have been reported in older subjects have mostly been associated with influenza, in certain epidemics of which staphylococcal infection has been conspicuous as the cause of pneumonia of a peculiarly grave and fatal character (Chickering and Park, 1919). Reimann (1933), who reported six cases, considered that 'primary staphylococcic pneumonia' is a clinical and pathological entity. The writer (Macgregor, 1936) published a pathological description and discussion

of ten cases, one of which was within the neonatal period, and concluded that staphylococcal pneumonia is 'an entity presenting distinctive pathological characters'. Smith (1935) reported an outbreak which affected several infants in a maternity hospital.

In most of the reported cases staphylococcus aureus was the organism responsible. The writer (Macgregor, 1936) had one case due to a strongly haemolytic strain of staphylococcus albus. Mixed infections with bacteria of other species are common and it has been assumed by many that the staphylococcal infection is a secondary development in lungs that are laid open to attack by the action of other organisms more commonly associated with pulmonary infections. This is no doubt the case when staphylococcal pneumonia complicates influenza, and in a number of other cases. But Reimann (1933) believed that the staphylococcal infection is often primary, and in six of the writer's (1936) ten cases no evidence of any associated infection was found.

In the present series there were 11 cases of staphylococcal pneumonia, including one which was placed in the group of pneumonia associated with prenatal aspiration, to which reference has already been made. This child, a premature infant, was born asphyxiated and died at 32 hours with evidence of aspiration of grossly infected liquor amnii and a

clear history of foetid waters. The ages of the other 10 infants ranged from 4 to 23 days; 5 died during the first week of life.

All these cases presented similar pathological characters and closely resembled those described by the writer in 1936, especially those in her Group 1, which included the earlier cases, before the development of empyema, which invariably occurred in the cases of longer duration. In every case in the present series pleurisy was present, with an effusion, usually moderate or small in amount, of slightly turbid, blood-stained serous or early purulent fluid, sometimes with a little fibrinous exudate, and many subpleural haemorrhages. The pneumonia occurred in one or more rather sharply defined areas of massive consolidation, always intensely haemorrhagic, and showing suppuration, either clearly visible to the unaided eye as ramifying pus-filled cavities or, when at an earlier stage, suggested by the moist and disintegrating appearance of the cut surface. Other parts of the lungs were usually free from pneumonia and there was no generalised bronchitis; if not collapsed owing to a pleural effusion, these parts were aerated though usually acutely congested and oedematous. Only in one case, in which there was a mixed infection, was any pneumonic consolidation found in parts that did not present the appearance

described.

Microscopic examination showed that the consolidation was due to a combination of massive haemorrhage and inflammatory exudation with a strong tendency to rapid suppuration. The bronchi formed the centres of the disturbance; their walls were destroyed by suppuration, which spread into adjacent alveoli, so that abscess cavities were formed which extended in ramifying fashion along the bronchi. Suppurative lymphangitis developed not only in peribronchial, but also in perivascular, septal and pleural lymph vessels, and from them suppuration spread out into adjacent lung substance. There was thus produced a most remarkable disorganisation of the lung. Everywhere throughout the affected parts immense numbers of staphylococci were found in large clumps. (Figs. 21 to 25)

In no case, except that of the youngest infant in the group, (to which reference was made above) was any evidence found of aspiration of foreign material into the lungs.

Seven of the babies in this group were premature, 4 were born at term. Three were delivered by Caesarian section. There was one case of dry labour, but as the child lived 11 days this was probably not of causative significance. The group included no forceps deliveries. Three mothers had toxaemia of

pregnancy; one had leucorrhoea. Two babies had intracranial haemorrhage, which was of intra-ventricular type in one. One child had a severe staphylococcal stomatitis, which was contracted from another baby who shared the same incubator. In no case was there any associated condition likely to have been a source of generalised blood infection, and no case presented any metastatic lesions.

Bacteriological examinations were carried out in every case in this group and in every case staphylococcus aureus was isolated from the lungs, and in many from the pleural fluid and blood also. In 10 cases no evidence was obtained of the presence of any other organisms. In one case Bact. coli communis was isolated from a consolidated area which did not show the appearance of staphylococcal pneumonia but that of a typical bronchopneumonia, and staphylococcus aureus from the characteristically affected part. A feature of all these cases was the remarkable numbers of staphylococci that appeared in the films, indicating an exceedingly heavy infection (Figs.24,25)

Discussion of the observations on staphylococcal pneumonia. These cases presented no difficulty in the matter of macroscopic diagnosis of pneumonia, and so distinctive was their appearance that it was almost always quite easy to recognise them as staphylococcal pneumonia at necropsy, before any further

investigation had been made. The only difficulty that occasionally arose was in distinguishing them from cases of staphylococcal infection of embolic origin. As can be inferred from the description given, the macroscopic appearance of the affected area was not unlike that of a septic infarct. It was, however, usually larger than infarcts commonly are in newborn infants; it was seldom wedge-shaped, as infarcts often are; though it usually reached the pleural surface it was less strictly peripheral in position than infarcts usually are; even when the areas were multiple they were never as numerous as is usual with embolic lesions; and there were no thrombosed arteries, no source of embolism and, in this series at least, no metastatic lesions elsewhere.

On microscopic examination the massive haemorrhage mixed with suppuration might suggest septic infarction. But there were no arteries blocked with emboli, no necrosis dependent on vascular occlusion, no bacterial emboli in capillaries. The inflammatory process centred in the bronchi and suppuration developed in and extended along them, though often it involved other structures in its spread. The microscopic diagnosis was therefore not difficult.

This type of pneumonia is indubitably due to an infection that enters the lungs by the bronchi. Some of its features, particularly its characteristic

localisation and the extraordinary heaviness of the bacterial infection, which is invariable, suggest that it might be caused by aspiration of septic foreign material into the lungs. Johnson and Meyer (1925) thought that staphylococcal infection of the lungs might be caused by aspiration of milk, which often contains staphylococci; and in one of the writer's previous cases (Macgregor, 1936) the history indicated this as a probable cause. In the present series, however, no evidence was obtainable either from the history or from the pathological study to suggest aspiration of milk or any other septic foreign material, except in the one case in which foetid liquor amnii was the obvious source of infection. In one case there was a clear history of infection from another baby who had a staphylococcal stomatitis.

(f). 'Lobular' or 'alveolar' (pneumococcal) pneumonia. Reference has been made above to a type of disseminated pneumonia described by Holt and McIntosh (1933), in which the patches bear no strict relation to bronchi and interstitial inflammation is absent, and to which theyapplied the term 'lobular pneumonia' as more appropriate than 'bronchopneumonia'. Holt and McIntosh asserted that this is the commonest form of pneumonia in infants under two years old. This has not been the experience of the writer, who has found that

the type of pneumonia much most often seen at necropsy in children under two years of age is true bronchopneumonia. The other type, so commonly seen in clinical practice though relatively seldom post-mortem, owing to its favourable prognosis - the 'alveolar pneumonia' of McNeil et alia (1929) - tends to be more localised in the older infants, bearing a closer resemblance to true lobar pneumonia. The writer has seen cases that fit Holt's description of disseminated lobular pneumonia, though seldom in infants over six months old, and with no great frequency in those under that age. Some of the best examples of it are to be found among neonatal cases.

In the present series there was a small group of 6 cases of this type. The babies' ages ranged from 3 to 27 days, all but one being over 10 days old. In the youngest child the pneumonia was at a very early stage and of small extent; in all the others it was severe and extensive. It occurred in well expanded lungs. The consolidation was patchy, the patches being of variable size and often large though seldom extending to a whole lobe. Consolidation within the patch was very complete and uniform, so that both on the outer surface and on section the affected areas stood out above the level of adjacent aerated substance, a feature seldom noted in bronchopneumonia owing to associated secondary collapse. The areas

were remarkably sharply defined, often having a clear, straight margin where they abutted upon aerated tissue. They were red, uniform in colour and consistence, and on section presented a much drier surface than that in typical bronchopneumonia; the appearance, but for the patchy distribution of consolidation, was reminiscent of lobar pneumonia at the stage of red hepatisation. Pleurisy was not present in any case.

Under the microscope the pneumonic areas showed complete and uniform consolidation, all the alveoli being fully expanded and filled with exudate (Fig. 28). The exudate was cellular, rich in polymorphonuclear leucocytes (Fig. 28); a little fibrin was present in some cases, mostly in the older children; red blood corpuscles mingled in varying numbers with the exudate, but only in the youngest patient, who was 3 days old, was there any considerable amount of haemorrhage (Fig. 26). The exudate was very uniform in all parts of the consolidated area and was not denser in the peri-bronchial zones as it is in typical bronchopneumonia. The bronchi contained exudate similar to that in the alveoli and shared in the general congestion, but otherwise they showed little inflammatory change. Their walls were not swollen or infiltrated, and even the epithelial lining was usually intact (Fig. 27). The sharply defined margin of

the consolidated areas was due to their being bounded in many instances by interlobular septa, and beyond the boundary of the patch the lung substance was well aerated and did not show either bronchitis or outlying patches of consolidation related to bronchi (Fig. 26). These cases did not show any true bronchitis or interstitial inflammation. The consolidation had not a strict bronchial or peri-bronchial distribution but occurred in lobules, or more often in groups of lobules. These features of the pathological picture served to separate them from the group of typical bronchopneumonia.

In this group 2 babies were premature, 4 were mature. There were 2 breech deliveries and 2 with forceps. One child, who died on the 15th day, had slight intracranial haemorrhage, which was not the direct cause of death. No others had any lesions apart from the pneumonia. The maternal histories contained nothing relevant.

Bacteriological examinations were made in all six cases in this group and resulted in the isolation from each of them of a pneumococcus in pure culture. The pneumococcus was of Type I in two cases; of Type II in three cases; of Type III in one case.

Discussion of the observations on 'lobular' (pneumococcal) pneumonia. It is of interest that these cases, in which the pathological characters were such

as to separate them decisively from the group of typical bronchopneumonia, to which they bore an obvious, though superficial, resemblance, were found to be distinctive bacteriologically also, forming a group that contained all the examples of pure pneumococcal infection that occurred in the whole series, and no others. This justifies the suggestion that the particular type of pathological process described is characteristic of pneumococcal infection in the newborn. It is not a typical lobar pneumonia, no case of which occurred in this series. It has not the massive lobar consolidation limited, as it usually is in adults, to a single large area, but occurs in multiple smaller patches. It has not the richly fibrinous exudate or the accompanying fibrinous pleurisy so characteristic of true lobar pneumonia. But it does present, within the area of each patch, a picture that bears a close resemblance in certain essential features, to that of lobar pneumonia: a massive uniform alveolar consolidation lacking clear relation to bronchi; the bronchi affected by the inflammation only to a minor extent; consolidation limited to certain well-defined areas and not accompanied by outlying peri-bronchial patches; and an absence of interstitial inflammatory infiltration.

It would appear both on pathological and on bacteriological grounds that this type of pneumonia in

the newborn corresponds to lobar pneumonia in older people. The difference between the two presumably depends upon the reaction of which the infected person is capable. According to Lauche (1927) and others whose work was reviewed by Hadfield and Garrod (1938), typical lobar pneumonia can occur only in persons who have been sensitised to pneumococcal products, that is, in older persons who have had previous pneumococcal infections, or in newborn babies who have been sensitised passively in utero when their mothers suffered from lobar pneumonia during pregnancy. The present series contained no case of a child whose mother had lobar pneumonia during pregnancy, and the writer has never seen such a case, or any example of typical lobar pneumonia in a newborn infant. The modern opinion that allergy (in contrast to anaphylaxis) does not depend on the presence of a circulating antibody and therefore cannot be passively transferred, suggests a difficulty in accepting Lauche's theory of passive sensitisation of the foetus. But, as has already been mentioned, there is a considerable weight of evidence to show that the occurrence of typical lobar pneumonia does in some way depend on previous pneumococcal infection. It is suggested that the type of pneumonia now under consideration may be regarded as characteristic of pneumococcal pneumonia in a subject who has had no previous pneumococcal infection.

There is a difficulty in devising a suitable name for this type of pneumonia. It is not broncho-pneumonia. It is not lobar pneumonia. It is not croupous pneumonia, for that name implies a richly fibrinous type of inflammation, which these cases do not show. The term 'lobular pneumonia' is ambiguous because it has for long been used as a synonym for bronchopneumonia. McNeil, Macgregor and Alexander (1929) suggested the term 'alveolar' pneumonia to designate pneumonia of the lobar or croupous type in children, in whom it is so often not of lobar extent. This term, which indicates that the inflammation is alveolar rather than bronchial, and avoids reference to the gross distribution or extent of consolidation, might suitably be applied to the cases under consideration. It has the further advantage that it indicates the essential identity of this type of pneumonia in the newborn with the better known and more typical forms of pneumococcal pneumonia in older infants, children and adults.

GROUP 4. Septicaemia with secondary involvement of the lungs (haematogenous infections).

In a group of 18 cases the inflammatory changes in the lungs were regarded as part of a generalised septic infection that originated elsewhere. The group does not include cases in which there was evidence of septicaemia or lesions due to blood-spread infection in other organs secondary to pneumonia, but only those in which the lung lesions were regarded as secondary and due to blood-spread infection. The changes in the lungs in these cases were of three different types.

(a). Focal areas of consolidation unrelated to bronchi and having the scattered distribution of embolic lesions but without necrosis and suppuration, sometimes coalescing into larger diffuse areas of rather indefinite consolidation, occurred in 3 cases, in babies aged 22, 27 and 28 days. The right of these to be regarded as examples of infection carried to the lungs by the blood might be disputed, as the evidence provided by the pathological character of the lesion was not conclusive. They were so regarded because the changes in the lungs did not correspond to any of the categories of pneumonia heretofore described in this study; because they corresponded to the description of metastatic infection given by Chase (1935); because in each case there was an obvious source of generalised

blood infection (umbilical sepsis in two, septic dermatitis in one); and because in each case a pure growth of streptococcus haemolyticus was obtained from the blood and from the lung.

(b). Typical embolic lesions - pyaemic abscesses and septic infarcts - occurred in 9 cases in which the ages ranged from 4 to 20 days. These lesions require little description as they differed in no way from similar lesions in older persons. Suppuration was always present and usually well advanced. Pleurisy occurred in every case, either with a viscid purulent exudate, seldom copious, or with effusion of thin turbid blood-stained fluid and a little fibrin. Microscopic examination showed the relation of the lesions to bacterial emboli in capillaries or septic embolism of larger arterial branches. (Fig. 29)

(c). Pleurisy with septic lymphangitis, a less familiar type of lesion, occurred in 6 cases. A septic pleurisy resulted from septicaemia and led to secondary invasion of the lungs by way of the lymph vessels, sometimes going on to suppuration. The ages of the babies ranged from 4 to 22 days, all but one being under one week. The pleurisy always took the form of a viscid purulent exudate, usually scanty, without recognisable fibrin. Involvement of the lungs was often not detectable at necropsy, but sometimes slight consolidation was suspected, and in one case

small subpleural abscesses were visible. The lungs were intensely congested.

Microscopic examination showed a cellular exudate, rich in polymorphonuclear leucucytes, on the pleural surface. The pleural lymph vessels were widely dilated and filled with similar inflammatory exudate. Lymph vessels accompanying the pulmonary veins in the interlobular septa were likewise involved to a variable distance from the pleural surface. In the more severe cases this lymphangitis had spread to the perivascular lymphatics of pulmonary veins deep in the lung substance (Figs. 30-33). In the slighter cases the inflammatory process had not spread beyond the lymph vessels, but in those of greater severity it had produced dense infiltration of the septa and perivascular tissue, and consolidation in adjoining alveoli. No case showed extensive consolidation of the lung substance. Several showed incipient or established suppuration; the abscesses developed under the pleura in relation to pleural lymphatics, or in the interlobular septa (Fig. 31).

In all these cases the inflammatory changes in the lung were entirely dependent on and secondary to the pleurisy. Several additional cases, which showed septic lymphangitis with pleurisy of the type described but accompanied by pneumonia or embolic lesions due to direct involvement of the lung substance by way of

the bronchi or blood stream, are not included in this group.

In the group of haematogenous infections as a whole, 6 babies were premature and 12 mature. The ages ranged from 4 to 28 days, 8 being under one week. Pleurisy with lymphangitis was commoner in the younger children, pyaemia or septic infarction in those over a week old. The primary focus responsible for the generalised infection was established in 10 cases in which infection was received after birth. It was umbilical sepsis in four cases, septic dermatitis in five, and suppurative otitis media in one.

In one case the history was strongly suggestive of intra-uterine transplacental infection. The mother had haemolytic streptococcal septicaemia before parturition. The baby died on the fourth day with haemolytic streptococcal septicaemia and pleurisy. Although the child survived a little beyond the limit of three days set by Hess-Thaysen (1914) and others for intra-uterine infections, transplacental transmission probably occurred in this case. It was the only case in the whole series in which any really suggestive evidence of this was found.

In another case infection from the mother was suggested by the history, but the evidence that it occurred before birth was not convincing. The mother had pyelitis due to an infection with Bact. coli. The

baby died on the seventh day of septicaemia with meningitis and pleurisy due to an infection with Bact. coli of the same type as that of the mother. This organism was obtained from the cerebro-spinal fluid of the child during life as well as from material collected after death. These facts do not prove prenatal infection. Even assuming that the two strains of Bact. coli were the same, there was an obvious possibility that the child might have received the infection from the mother after birth. The child's survival for a week makes intra-uterine infection very doubtful.

Associated metastatic lesions in other parts of the body were found as follows: meningitis in 5 cases; abscesses in the kidneys in 2 cases; endocarditis and abscess in the myocardium, each in 1 case.

The maternal and obstetrical histories showed that there were 5 deliveries by forceps, 3 breech presentations, 1 case of placenta praevia, and 1 case of Caesarian section. Most of the complicated labours were in cases in which the child survived for more than a week, so probably had no bearing on the infection in the child. One mother had streptococcal septicaemia before parturition; one had pyelitis; two had leucorrhoea. All the rest were healthy. Apart from the two cases already discussed, there was nothing in any of the histories to suggest infection of the

child before birth.

Bacteriological examinations were carried out in all the 18 cases and in each case resulted in the isolation of a single type of organism in pure culture. Streptococcus haemolyticus was obtained in 5 cases; streptococcus viridans in 1 case; staphylococcus aureus in 6 cases; coliform bacilli in 6 cases. Blood cultures were made in 11 cases and in 9 produced growths of the same organisms as those obtained from the lungs, but in 2 were spoiled by post-mortem contamination.

Discussion of the observations on haematogenous infections of the lungs. Of the cases attributed to haematogenous infection only those described as 'pleurisy with septic lymphangitis' require further comment. This type of lesion appears to be almost peculiar, if not to the newborn, at least to very young infants. In older subjects the pleural lymphatics often participate in pleurisy, but deep penetration of the infective process into the lung along the lymph vessels of the septa and pulmonary veins (i.e. the lymph vessels of the deep set) is, in the writer's experience, very unusual.

There is an anatomical reason for this. Miller's classical work (1919 and 1936) on the pulmonary lymphatics showed that the pleural lymphatic plexus communicates freely with the lymph vessels that

accompany the radicles of the pulmonary vein, especially those that run in the interlobular septa. At the junction of the superficial (pleural) and deep (venous) lymph vessels there are valves which point (open) towards the pleura. The presence of these valves 'precludes the flow in the pleural lymphatics from entering the lung'. The valves thus form a barrier against the ready passage of infection from the pleura to the lung. Hewat (1938), referring to tuberculosis, stated that 'it is - - - a well-known fact that pleural infections - - - do not spread to give rise to intra-pulmonary disease'. This appears to be equally true of acute infections of the pleura, even of empyema.

Newborn babies, however, provide an exception to this general rule. In them invasion of the deep lymphatics of the lung from the pleura is not uncommon. In this series it was seen not only in cases of pleurisy due to septicaemia but in some others with septic pleurisy. The writer has seen it in infants beyond the neonatal period but never in one more than a few weeks old. This suggests that in the very young the valves in the lymph vessels provide a less efficient obstacle to the inward flow of lymph from pleura to lung.

In this connection Miller's observations are of great interest. He carried out enumerations of the

valves in the pulmonary and pleural lymph vessels in a newborn infant and in one of nine weeks and reported that 'when the lung of the nine-week-old child is compared with that of the new-born child - - - it is found that an important change has taken place - - - more valves are present'. His conclusion was that 'it is not improbable that in the nine-week-old child new valves had developed'. It seems likely from this work that the development of the valves in the lymph vessels of the lung and pleura is incomplete at birth and continues for some time thereafter. If this is so it offers a satisfactory explanation of the occurrence of this unusual pathological process in very young infants.

Note on Pleurisy. Pleurisy was present in a considerable number of cases, but it is noteworthy that these cases, almost without exception, were of one of two types: either they were cases of septicaemia in which the pleura was infected from the blood and not from the lung, or they were cases with suppuration in the lung due to any cause. Pleurisy occurred in every case of staphylococcal pneumonia, in most cases of haematogenous infection, and in occasional cases in other groups when either septicaemia or pulmonary suppuration was present. It was very unusual under any other circumstances, no matter how extensive and massive the pneumonia might be. This is in contrast to its comparative frequency in severe pneumonia of all types in older infants and children.

The pleural exudate was usually either a thin, often blood-stained serous fluid, or viscid semi-purulent exudate which did not adhere to the serous surface. Dry fibrinous pleurisy was not seen, and with serous effusions fibrin, if present at all, was always small in amount. Apparently the acute inflammatory reaction in the newborn does not readily produce fibrin. No case of true empyema occurred during the course of the investigation.

TABLE 1.

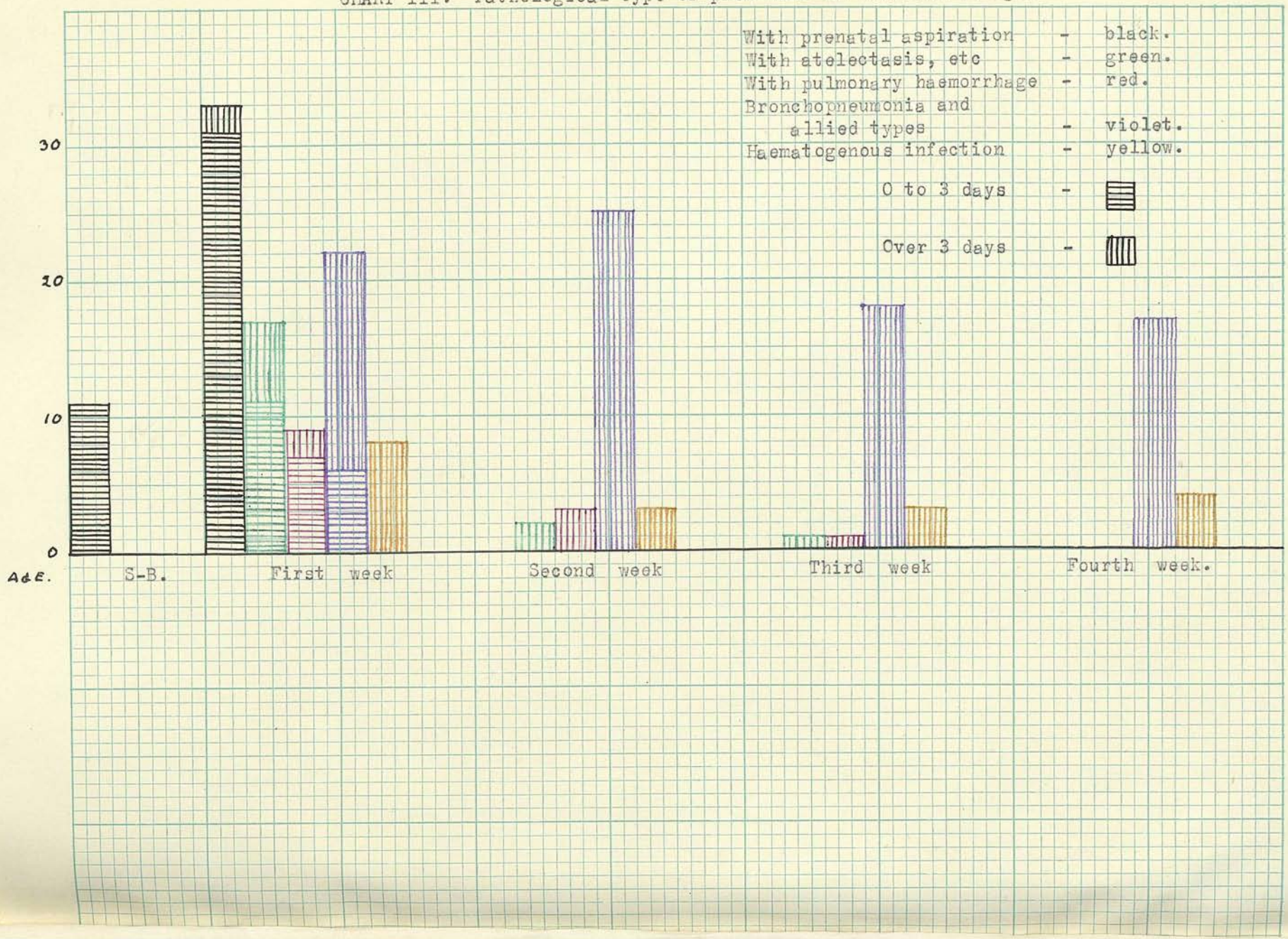
Age in relation to pathological type.

TYPE OF PNEUMONIA.	Age in days.						
	S.B.	0-3	4-7	8-14	15-21	22-28	Total
Prenatal aspiration	11	31	2				44
Atelectasis, etc		11	6	2	1		20
Haemorrhage		7	2	3	1		13
Postnatal aspiration		1	1	5	1		8
Bronchopneumonia, bronchitis, hypostatic pneumonia		4	10	17	12	15	58
Staphylococcal pneumonia			5	1	3	1	10
Alveolar pneumonia		1		2	2	1	6
Haematogenous infections			8	3	3	4	18

Note on the relation of age to pathological type of pneumonia. Table 1 presents a summary of facts that have already been given with regard to the age incidence of the various pathological types of pneumonia. The first week is divided into two periods in order to show the remarkable difference between the first three days and the later days as regards the prevalent types. It is to be noted that cases in which pneumonia was associated with prenatal aspiration, congenital atelectasis or massive pulmonary haemorrhage were all much most frequent in the first three days and seldom occurred after the first week. This is most strikingly exemplified by the group with prenatal aspiration, which practically disappeared after the third day. On the other hand cases with evidence of postnatal aspiration, bronchopneumonia and allied types, and haematogenous infections were seldom seen before the fourth day, some of these types being commonest after the end of the first week. This is well shown in the case of bronchopneumonia, which began to be important on the fourth day and maintained a comparatively high frequency till the end of the fourth week. It was much the commonest type in the second half of the neonatal period. (Chart 3.)

These facts may be taken to mean that cases in these latter groups were for the most part due to

CHART III. Pathological type of pneumonia in relation to age.



infection acquired after birth. The earlier age incidence of the former groups does not so clearly indicate prenatal infection, as the problem with regard to them is complicated by various factors to which some reference has already been made, and which will be discussed further in a later section.